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THE TREATMENT OF BRONCHIAL ASTHMA BY DORSAL SYMPATHECTOMY

DIRECT AND INDIRECT

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THE essential factor in causation of asthma is spasmodic contraction of bronchial muscles. It is a matter of paramount importance, therefore, to ascertain the exact source and the character of bronchial innervation. The current views on this subject may be summarized as follows: The smooth muscles of the bronchi derive their nerve supply on each side from the pulmonary plexus; the latter consists of two divisions—anterior and posterior—respectively adjacent to anterior and posterior aspects of the hilum of the lung. Both the vagus and the sympathetic contribute branches to the plexus; the vagus is held to be the constrictor or the catabolic nerve of the bronchial musculature, while the sympathetic is regarded as a nerve exerting anabolic or dilator action. Both nerves have central connection with the respiratory center in the medulla. The sympathetic branches reach the plexus through the connector cells which lie in the third and fourth thoracic segments of the cord; from there connector fibers in animals pass to the stellate ganglion; in man they appear to end in all three ganglia of the cervical sympathetic. From these the excitor fibers pass to the pulmonary plexus in the cardiac branches of the sympathetic.[1] The sympathetic dilator function is thought to be manifested by the effect of adrenalin injection during paroxysms of asthma, the suprarenal bodies being closely allied to the sympathetic both developmentally and functionally.

In the light of the recent investigations this conception of the bronchial innervation cannot be accepted in its entirety. In the first place, due prominence must be given to an important anatomic structure, namely, the sympathetic thoracic chain with its twelve ganglia (occasionally only 10 or 11 ganglia are present), and numerous afferent and efferent rami. This structure is situated along the necks of the ribs, the ganglia being placed directly in front of the corresponding rib. From each ganglion seven to nine rami proceed posterolaterally to join the under surface of intercostal nerve in the space immediately

above. Some of these communicating branches are myelinated* and some are nonmyelinated. From the second, third, and fourth thoracic ganglia branches proceed medially to join directly the pulmonary plexus; from all the

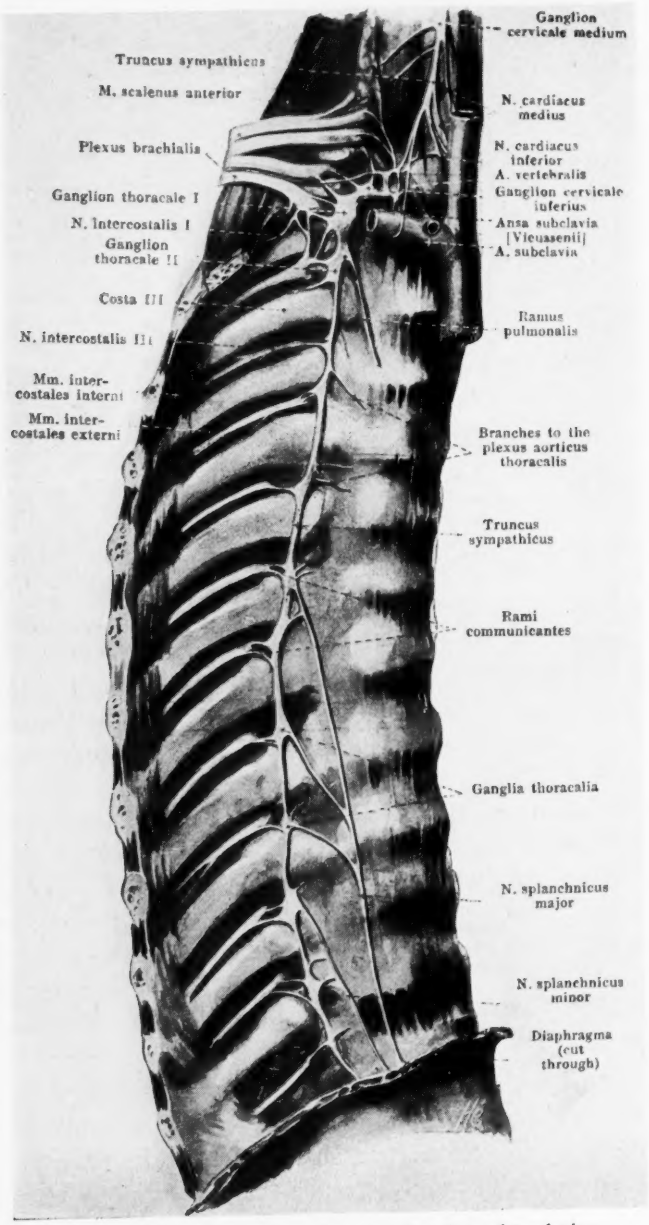

FIG. 1.—Right thoracic sympathetic trunk. Anterolateral view. (Spalteholz.)

* The term "preganglionic fibers of Langley" is best avoided inasmuch as Kunz and others have demonstrated the existence of both ascending and descending motor tracts in the myelinated rami.

ganglia, especially the upper five, branches also proceed to the aorta to assist in the formation of the thoracic aortic plexus, and from there they pass again to the pulmonary plexus.[2] With regard to the cervical sympathetic, there is clear evidence that the branches conveyed by it to the pulmonary plexus are indirectly of thoracic origin. They pass from the upper six thoracic ganglia along the communicating rami above mentioned, then joining the anterior roots of the thoracic nerves they are continued in the spinal column as far as the third and fourth thoracic segments; thence they travel via the upper intercostal nerves and the thoracic sympathetic trunk[3] to the cervical sympathetic ganglia and finally reach the bronchi in the cardiac branches of the latter[4] (Fig. 1). It may be added that some fibers ascend along the main thoracic sympathetic trunk directly to the cervical ganglia without establishing synapses with the connector cells in the cord.

It will be thus seen that the whole of the sympathetic bronchial innervation is derived from thoracic source, either directly or indirectly; also that the greater bulk of it is contained in the communicating rami joining the intercostal nerves.

Further, it must be emphasized that sensory fibers are present in the sympathetic rami in addition to the motor axons, whether constrictor or inhibitory. Leriche,[5, 17] who was very largely responsible for the introduction of periarterial sympathectomy, describes its after effects in the following way: There is an initial stage of vasoconstriction which lasts from two to 18 hours; this is followed by sudden dilatation of the artery which lasts 16 days; after that period the circulation returns to normal. Similar changes take place in the opposite limb. The regularity of vasoconstriction followed by vasodilatation with similar sequence of events on the opposite side is proof, he says, of the existence of afferent or sensory fibers in the outer sheath of large blood vessels.[5]

The sympathetic action is entirely reflex and from the practical point of view it matters little whether the sensory or motor branch of the reflex arc is severed; in neither case will exciting stimuli provoke any response. Even if one considers an ordinary skeletal reflex like a knee jerk, one realizes that motor action can never take place unless the sensory apparatus is preserved; where the latter is destroyed, as for instance in tabes dorsalis, the reflex cannot possibly be elicited.

On the other hand, one may hope by the destruction of the motor arm of the reflex arc to inhibit sensation of pain. Thus, for instance, severance of the upper sympathetic cervical trunk, which is a purely motor nerve, has been practised very widely for the relief of angina pectoris.[6]

It is important to note that all the sensory or afferent dorsal sympathetic pulmonary fibers are contained in the communicating branches passing to the intercostal nerves.

Finally, the conception of the vagus being the constrictor bronchial nerve, *i.e.*, the asthmatic nerve *par excellence*, cannot be accepted without criticism. The only evidence in support of this view are the experiments of Brodie and

Dixon.[8] They found that stimulation of the vagus nerve in animals was followed by contraction of the bronchial muscles, while stimulation of the cervical sympathetic was followed by no response. They themselves, however, admit the existence of dilator fibers in the vagus, inasmuch as stimulation of the latter after administration of muscarine and pilocarpine was followed by dilatation of the bronchi. Further, their experiments were confined to the cervical sympathetic system and not the thoracic, which is the true source of the sympathetic supply of the bronchi; nor did they exclude reflex possibilities of bronchial dilatation or constriction, following manipulations of the neck, and in addition their results were arrived at by observing the effects of forcible inflation and deflation of the lungs through the trachea and not by registering the exact degree of distension and collapse of the alveoli which is the normal course of events in respiration.

In this connection Gask and Ross[9] very appropriately remark: "No conclusions with regard to the sympathetic system in man can be derived from the experiments on the lower animals whose sympathetic system differs in many respects from the human. Only careful analysis of the information obtained by accurate observation of patients, especially of patients on whom an operation has been performed upon some portion of the sympathetic system, will bring to light facts which can be proved by no other method of research."

The conclusions of Brodie and Dixon[8] are not borne out by results of clinical observation. In many conditions—pathologic and operative—the circumstances so combine as to amount unwittingly to an actual experiment upon the vagus. As a typical instance, one may consider the second or irritative stage of tuberculous meningitis. The characteristic feature of this stage is slow action of the heart, as contrasted with high temperature, convulsions, carinated abdomen, *etc.*, the bradycardia being due to direct irritation of the vagus center. Yet in spite of the vagus being thus singled out and specifically irritated by the presence of pathologic exudate, bronchial asthma has never been observed. On the contrary, the respirations during this stage are free and deep—"rarely altered from the normal" (Osler[10]).

Again, it is a recognised rule in the course of operations on the esophagus to paint the vagus with 10 per cent cocaine; failure of this precaution, prior to handling of the vagus, was followed by dangerous slowing of the heart, but never by paroxysms of bronchial asthma.

There are also other considerations which strongly militate against the supposed constrictor action of the vagus. Fraser,[11] writing on surgical aspects of certain disturbances of the involuntary nervous system, particularly stresses the point that in the course of evolution the sympathetic system, being an essentially motor or constrictor structure, was acquired first, while the parasympathetic nerves, being by nature inhibitory or relaxing, were evolved at a much later date. Although he admits that in certain parts of the body the same system may contain both sets of fibers (for instance, the sympathetic is both—motor and relaxing—nerve for the large intestine from the ileocecal

valve to the lower end of pelvic colon), yet, as a general rule, he states, where the involuntary nerve supply is double the sympathetic always maintains its phylogenic constrictor function, while its parasympathetic antagonist (the vagus in the case under consideration) invariably exercises inhibitory influence.

Carmichael and Fraser[12] have demonstrated in their recent work that stimulation of the vagus results in actual liberation of acetylcholine around the vagal nerve ends; while stimulation of the sympathetic is followed by production of a substance chemically similar to adrenalin in the immediate proximity of the nerve ends. In view of the well known depressor and relaxing effect of acetylcholine on involuntary muscle it appears utterly impossible for the vagus to act as a bronchial constrictor. As a matter of fact, no lesion of the vagus—paralytic or irritative—has ever clinically been found to be accompanied by any vestige of signs of asthma. This holds equally true whatever the nature or the position of the vagal lesion—whether due to pressure of tumor or meningeal exudate, or to injury or to peripheral neuritis, and whether affecting the vagal nucleus or the trunk.

One is forced to the conclusion that the vagus is not the catabolic or the constrictor bronchial nerve, at least not in man. It follows from this, indirectly, that the constrictor fibers must perforce be contained in the sympathetic.

Morphologic considerations substantiate this view inasmuch as the sympathetic nerves are accelerators of the heart and constrictors of the alimentary canal from the pylorus to the ileocecal valve. The occurrence of signs of general sympathetic disturbance in asthma, such as polyuria, urticaria, *etc.*, indicates a state of motor irritability of the entire sympathetic system. Study of certain aberrant forms of asthma also lends color to the constrictor conception of the sympathetic. So called renal asthma, for instance, constitutes a very curious pathologic phenomenon; its occurrence and some of its features cannot be satisfactorily accounted for except on the assumption that the bronchial sympathetic fibers are endowed with contractor power: the three splanchnic nerves which form the chief nerve supply of the kidney arise from the thoracic ganglionated trunk, *i.e.*, the same structure which is connected with and is responsible for the bronchial sympathetic supply; the pulse in renal asthma is rapid—not slow as one would expect had the reflex action taken place through the vagus. The latter remark applies with equal force to the cardiac asthma, also to the other types of reflex asthma.

With regard to the action of adrenalin, it is true enough that an hypodermic injection would relieve the spasm, but it is equally certain that were adrenalin applied directly to the bronchial muscle it would produce constriction of the latter in the same way as it does in the case of blood vessels, uterus, intestinal muscle, *etc.* The action of the adrenalin must be, therefore indirect.[13, 14]

It will be gathered from the foregoing considerations that the rationale of dorsal sympathectomy for relief of asthma is twofold:

(1) Sympathectomy is a sure method of severance of all sensory dorsal

sympathetic stimuli, thus throwing out of action the motor half of the reflex arc.

(2) It implies direct destruction of the bronchial constrictor nerves (especially those belonging to the second to sixth dorsal rami).

Technic.—There are three methods of direct and two methods of indirect dorsal sympathectomy applicable for treatment of bronchial asthma.

(1) *Anterior Sympathectomy by the Method of Royle.*[15]—An incision is made parallel to the clavicle; the attachment of the sternomastoid is partly severed from the clavicle; the deep cervical fascia and the omohyoid are divided after securing the transverse cervical vessels and the scalenus anticus and the phrenic nerve are defined by gauze dissection. The attachments of the scalenus to the first rib are cut through, the subclavian artery thus exposed is mobilized and retracted downwards and forwards. The fascia of Sibson is incised along the inner border of the first rib; the dome of the pleura brought into view is retracted forwards and inwards after freeing the pleura from the first three thoracic vertebrae. The lowest cevical ganglion is found on the neck of the first rib; the thoracic trunk is followed down as far as the third thoracic ganglion and at that point is cut across. All the rami are divided from below upwards until the inferior cervical ganglion is reached and the trunk is severed just below the latter.

(2) *Posterior Sympathectomy by the Method of Adson.*[16]—The incision is made from the spine of the sixth cervical vertebra to the spine of the fourth thoracic. The attachments of the superficial muscles of the back are cut through and the erector spinae and the splenius capitis muscles are split longitudinally exposing the transverse processes and the adjacent upper three ribs. The transverse process of the second vertebra is severed and about two inches of the second rib are removed subperiostially. The pleura is gently peeled off the necks of the first three ribs and the bodies of the upper three thoracic vertebrae. The thoracic trunk is then found on the neck of the second rib and is divided below the second thoracic ganglion and is followed upwards with division of all intervening rami to a point just above the inferior cervical ganglion where the trunk is cut across again.

Both these methods tax the patient rather heavily and they imply severance of sympathetic supply of all the other thoracic organs as well as of the rami joining the brachial plexus.

(3) *Posterior Rami Section by the Method of Leriche.*[17]—The approach is on similar lines to that of Adson but the level of the operation is lower down. The incision is made close to the spine two spaces above and below the selected interspace; the muscles are split longitudinally and the articular and the transverse processes with the costal tubercle of the corresponding rib are exposed. The transverse process is severed at its base; the intercostal nerve of the space is retracted upwards and the rami are recognized as tense threads entering the under surface of the nerve; they are sectioned one by one. This method is obviously limited in its application and is suitable only for comparatively mild cases.

(4) *Destruction of the Rami by Injection of Absolute Alcohol.*[18]—The procedure is as follows: A point is selected 4 cm. away from the spine, preferably in the third or fourth interspace; the lower border of the rib is felt by the tip of the finger and the needle is introduced directly to the inferior margin of the rib; from this point the needle is directed 45° inwards, forwards and downwards to the depth of about 2 cm. Every precaution is taken to guard against perforation of the pleura; the needle is now connected with a syringe containing 2.5 cc. of absolute alcohol and the latter is injected by a series of small spurts. Occasionally the transverse process is unusually bulky and obstructs the desired position of the point of the needle; the latter must be then directed in such a way as to pass immediately in front and below the process; should that be found impossible the space immediately above has to be injected instead. As a rule, four injections, one a week, are given followed after a month's rest by another series of four, should any trace of asthma still persist. There is rarely any radical improvement until after the second or the third injection. The first injection is usually associated with a good deal of shock, necessitating a few hours' rest in bed.

Abbreviated Case Reports

Case I.—Miss B., aged 22. Subject to bronchial asthma since age of six; unable to pursue her studies; attacks temporarily relieved by morphia gr. ¼. Some improvement after course of autogenous vaccine. Four injections of absolute alcohol into the fifth and sixth right interspaces and fourth and sixth left interspaces. Total disappearance of asthma; no recurrence for the last two years.

Case II.—Mr. A., aged 64. Intractable asthma of twelve years' standing; forced to give up business. Resection of septum three years ago with alleviation of symptoms but with no relief from nocturnal attacks. Three injections of absolute alcohol in both third interspaces and the fifth right space. Marked improvement after second injection. Complete cessation of asthma for the last seven months.

Case III.—Mr. R. T., aged 31. History of severe asthma of four years' duration. No relief from morphia, adrenalin, peptone or autogenous vaccine. Dyspnea almost unbearable. Absolute alcohol injection into the third and fourth rami on each side; great improvement after the second injection. Complete disappearance of asthma; absolutely free for the last three and one-half years.

Case IV.—Miss W., aged 61. Long history of bronchial asthma; emphysema of the right side with collapse of the left lung. Nine injections of absolute alcohol spread over a period of eight months. Entire disappearance of asthma; no return for the last twelve months.

Case V.—Mr. C., laborer, aged 49. "Incurable" bronchial asthma since age of 12; never entirely free; unable to follow his employment for any length of time. Five absolute alcohol injections given at weekly intervals. Has been perfectly free from asthma for the last two years.

(5) *Destruction of the Upper Portion of the Thoracic Ganglionated Trunk by Injection of Absolute Alcohol.*—Although the third and fourth thoracic segments are anatomically placed opposite the spines of the first and the second thoracic vertebrae, the bulk of their efferent fibers pass to the fourth and the fifth thoracic ganglia and the upper thoracic trunk via the third and fourth intercostal nerves[19]; the upper thoracic trunk, therefore, can be

effectively attacked either in the third or the fourth space, preferably in the third. Either novocaine or gas-oxygen anesthesia can be employed. The technic is as follows: the patient's spine is strongly arched backwards with the scapulae forcibly retracted so as to bring the selected rib (the fourth or the fifth) as near the surface as possible. The upper and lower costal margin are ascertained, bearing in mind that the plane of the junction between the manubrium and the gladiolus sterni (Ludwig' plane) is on the level of the disk between the fourth and the fifth thoracic vertebrae; at a point about three cm. from the middle line a sharp solid cutting needle is introduced down to the lower border of the rib and is directed 50° forwards, inwards and downwards until the transverse process of the corresponding vertebra is felt; the upper margin of the rib is then followed by the finger tip to a point directly opposite the level of the process. A strong needle of the lumbar puncture type but of shorter length is now introduced on the slant from below so as to strike the upper margin of the rib immediately under the finger tip. The needle is so placed that its point and the aperture lie immediately in contact with the upper border of the rib. The needle is now cautiously pushed upwards, inwards and forwards closely hugging the upper margin of the rib for a distance of about two and one-half to three cm. Although perforation of the pleura appears almost inevitable experience shows that it is easily avoidable provided the needle is closely applied to the upper boundary of the rib slightly on the posterior plane. When the needle has traversed about two and one-half to three cm. of the neck of the rib it is rotated to an angle of 90°—the orifice of the needle is now directly behind the thoracic trunk. Precautions are taken again to ascertain that the pleura is intact; one cc. of absolute alcohol is slowly injected and the needle is withdrawn. Roentgenographic screen may be used as an adjuvent to make the position of the needle certain. Should the pleura be punctured during the manipulation, no harm follows in view of the valvular character of the opening. The same procedure may be adopted for the third and the second interspaces but the maneuver is more difficult on account of the greater depth of the ribs. This method is rather a major undertaking when compared to the preceding one[4] but it has the advantage of reducing the total number of injections to two.

Abbreviated Case Reports

Case I.—Mr. J., aged 42, dentist. Severe spasmodic bronchial asthma of three years' standing; cardiac dilatation; totally incapacitated for last eight months. Autogenous sputum vaccine tried with no success; had been advised to give up practice. Injection of absolute alcohol into the upper thoracic trunk above the level of the fourth rib on both sides under gas-oxygen anesthesia. Gradual disappearance of asthma; chest entirely free in about a month after the injection; general condition much improved, the heart normal. No recurrence of asthma for the last six months.

Case II.—Mr. W., aged 35. Subject to bronchial asthma for last three years; forced to give up work; unable to sleep; great dyspnea. Injection of alcohol into the left upper trunk above the level of the fifth rib under local anesthesia; pleura inadvertently punctured on the right side—injection postponed. A week later the right side injected at the same level also under local anesthesia. Complete freedom from asthmatic attacks in about six

weeks after the second injection. Perfectly free for the last eight months, gained two stone in weight.

CASE III.—Miss L., aged 37. Severe bronchial asthma since age of seven; "spent the life sitting and gasping for breath." Under local anesthesia the right upper thoracic trunk injected above the level of the fourth rib; the same procedure ten days later on the left side. Great improvement after the second injection; has not been troubled with asthma since (for the last four months).

Generally speaking, the indirect methods, *i.e.*, based on absolute alcohol injection, are preferable to the open sympathectomy for the following reasons: the procedure is infinitely quicker, the risk practically nil, the condition of the patient is usually such as to preclude any direct operative interference; furthermore, total abolition of the sympathetic control is undesirable on account of the danger of subsequent development of bronchiectasis.

In the writer's series of 23 cases treated by absolute alcohol injection, complete relief was obtained in 75 per cent with varying degrees of improvement in the remainder. All the cases were of long standing intractable asthma. Eighteen cases were treated by Method 4 (13 with complete relief) and five by the Method 5 (complete relief in four cases). The resistant cases were chiefly those where emphysema and collapse of the lung were marked features. Perforation of pleura took place on three occasions with no serious consequences.

SUMMARY

(1) There is sufficient theoretical, pathologic and clinical evidence to show that the dorsal sympathetic nerves, especially the second, third, fourth, fifth and sixth rami, contain both contractor fibers to the bronchial musculture as well as sensory bronchial fibers.

(2) Both the rami and the thoracic trunk are accessible either for neurectomy or for neurolysis by absolute alcohol; the rami—immediately below the points of junction with the intercostal nerves, the trunk—above the level of the neck of the fourth rib.

(3) Bronchial sympathetic neurolysis by absolute alcohol has resulted in complete relief in 75 per cent of cases of severe intractable asthma treated.

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MESENTERIC VASCULAR OCCLUSION

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MESENTERIC vascular occlusion was first described in 1834 by Tiedeman. In 1847, Virchow described the pathology in detail. The clinical aspects of the subject were first brought to medical attention by the researches of Kussmaul and Gerhardt in 1863, and by those of Litten in 1875. Shortly thereafter Cohnheim, Cohn and others also published the results of their experimental and clinical investigations. Welch and his associates contributed to the knowledge of the pathology and reviewed the subject up to 1900. In the last 30 years numerous excellent papers have brought the subject more fully before the medical profession. Jackson, Porter and Quimby in 1904, Trotter in 1913, Ross in 1931, Loop in 1921, Larson[26] in 1931 and Meyer in 1931 are only a few of the outstanding contributors. There are also many case reports, most of which submit a successful operation.

Brady[4] stated that up to 1921 about 500 cases had been reported with only about 35 recoveries. Meyer[33] reported 92 additional cases up to 1931 with 39 recoveries. This is not as complimentary to recent medical knowledge as it seems, as there undoubtedly are a great many fatal cases which have not been reported.

Occlusion of the mesenteric vessels may result from four main causes according to Cokinis (quoted by MacCornack[28]). These are: (1) By trauma. (2) By external pressure. (3) By embolism and thrombosis. (4) By inflammatory or degenerative obliteration of their lumens.

The two most common causes are thrombosis (arterial and venous) and arterial embolism.[32] In arterial occlusion any affection that predisposes to thrombotic formation is of etiologic importance. Endocarditis, atheroma of the aorta, and arteriosclerosis, especially of the mesenteric vessels, are common causes.

Connors[8] states that he feels that arterial thrombosis in a manner similar to coronary thrombosis occurs all over the body. Arteriosclerosis is common in the mesenteric arteries and he believes that thrombosis, especially of the smaller arterial branches, is of much more frequent occurrence than its clinical recognition. Cawadias[7] reports a case with intermittent claudication for six years followed by angina pectoris with final thrombosis of the mesenteric vessels. Scherk[40] reports a case in which he feels the condition was caused by repeated attacks of lead poisoning causing arteriosclerotic changes leading to occlusion. Recently thrombo-angiitis obliterans has been reported as an important factor by Averbuck and Silbert.[2]

In venous thrombosis the condition may be primary in the mesenteric

veins and ascend into the larger radicals; or the reverse process may occur.[32] "Of especial importance in primary occlusion are intestinal changes that permit entrance of bacteria into the vascular channels such as enteritis, the puerperal state, phlebitis, appendicitis, pelvic disease and other suppurative conditions of the peritoneal cavity."[16] Hepatic disease, pyelophlebitis, syphilis and other conditions causing portal stasis or obstruction are mentioned as causes of secondary or descending thrombosis.[16] Larson (cited above) in a report of 36 autopsies found hepatic disease in 25 per cent. Venous thrombosis has been known to follow arterial embolism apparently because of the stasis thus produced.

The following reasons are usually given as the cause of the preponderance of superior mesenteric artery lesions: (1) It is larger than the inferior (about three to one). (2) It comes off above the inferior. (3) It comes off almost parallel to the aorta while the inferior comes off nearly at right angles. As a result it is more likely to intercept an embolus. The decrease in the size of the vessels in the lower ileum due to the numerous secondary loops may also play a part.

Physiology and *Pathology*.—Why does gangrene occur in the face of an apparently profuse blood supply? It seems that the vessels above and below should be able to carry on the work. That this is possible is well demonstrated in a case report by Chiene.[3] In a woman 65 years old with arteriosclerosis there was a complete fibrous obliteration of the superior and inferior mesenteric arteries and the celiac axis so that the entire bowel was cut off from its usual blood supply. This, without evident symptoms. The condition was noted at an autopsy.

Referring to occlusions of the superior mesenteric artery, Faber[35] states that the inferior mesenteric is a small vessel and is unable to take up the function of the larger. One infers from this that in occlusions of the inferior, the superior might help out simply because of its size. Boyd[3] states that the sudden anemia produced by an acute blockage of a branch of an artery sets up so violent a spasmodic contraction of the musculature of the bowel that the part becomes isolated from the neighboring circulation. This spasm aggravates the anemia to such a degree that the death of the affected segment of the bowel results very quickly. The spasm would of course depend on the extent and the rapidity of the occlusion, thus at once dividing the condition into an acute and chronic type. A slow extensive occlusion might be compensated while a small sudden clot might cause infarction. The pathology involved is the same no matter what the cause or part of the bowel, providing the occlusion is large enough to cause impairment of circulation to the part (Cohnheim).

Trotter reports three per cent mesenteric infarcts as being anemic, but pathologically according to Boyd[3] the infarct is always hemorrhagic. The area supplied by the vessel, if the blockage is arterial, is attempted to be supplied by the arteries above and below. In small occlusions or in gradual ones

this is successfully carried out. In others only sufficient blood is brought in from the arteries to cause the part to become congested.

The portal system has a certain pressure which is kept up by the pressure in the arteries. In an arterial occlusion, the venous supply of that part immediately drops to nil. There is, therefore, less pressure here than in the portal vein and the blood stagnates instead of passing normally. The area becomes overloaded with blood which is brought slowly to it from the adjacent arteries. Welch and his associates proved that the blood really came from the arterial capillaries and not from venous reflux as might be expected. This blood cannot escape and causes a hemorrhagic infarct. In venous occlusion, the pathology is evident. The blood has no outlet and there is a retrograde thrombosis of the arteries. The part affected is thickened, dark red to almost black in color, and soon becomes gangrenous. The limits are usually sharply defined but the demarcation may be more gradual.[3] The entire bowel wall is stuffed with blood, the mucosa is necrotic and may be ulcerated. The lumen contains thick tarry blood. The serous coat may be covered by an inflammatory exudate and the peritoneum contains bloody fluid. There may even be general peritonitis. The mesentery is thickened and may contain large hemorrhagic patches. The veins are swollen and engorged. The glands are also swollen and may be hemorrhagic. Boyd[3] states that there may be occlusion of the terminal arterioles with no signs of occlusion until the bowel is opened. In one case he found large hemorrhagic patches throughout the lower part of the small intestine with no lesion in the mesenteric vessels.

Surgical Pathology (Gross).—From a surgical standpoint the best gross description found by the writer of the appearance of mesenteric thrombosis at operation is by Loop.[27] (1) "Transparent, sticky, peritoneal fluid, amber or blood tinged, and without coagulated lymph." (2) "Cyanosed, plum colored, soggy, edematous intestine, with glistening peritoneum free from adhesions, its lumen relaxed (not distended) to large caliber, lying inert within the abdominal cavity, with no tendency to crowd out of the incision, held down by the weight of the fluid in its lumen but containing little gas. The mesentery forms a thick doughy mass dragging down over the pelvic brim as though adherent." Actually it is delivered with ease. Other writers have referred to the bowel as resembling a rubber hose.

Amount of Small Intestine Necessary for Life.—Flint[15] states that to lose the use of more than one-third to one-half of the small intestine is usually fatal. Meyer[33] states that recovery has occurred after practically complete removal of the small intestine. Wulsten[45] reports a recovery after removal of 360 cm. and Sjovall[42] a successful resection of 450 cm. or 90 per cent of the small bowel.

Frequency and Mortality.—Mesenteric vascular occlusions are considered to be quite unusual. Of 235 cases of obstruction, Cornell[9] stated that there were five cases of mesenteric thrombosis with only one survivor. Koslin[24] reported seven cases in 185 instances of intestinal obstruction with no recoveries.

Morton[34] reported 105 cases of obstruction with five cases of mesenteric thrombosis and four deaths, Loop[27] nine cases with one recovery and Dunphy and Zollinger[13] five cases with one recovery. The Binghamton City Hospital records show eight authentic cases with one recovery in the last ten years. Various authors have placed the mortality from 57.6[43] to 95 per cent.

Necessity for Surgical Intervention.—Meyer[33] states that in abdominal claudication the condition is entirely medical. From the pathology it is evident that unless there is insufficient circulation for life the condition will adjust itself. He found nine instances of spontaneous recovery in 92 cases. In six of these exploration alone was done. Rost,[38] Echemendes and Garcia,[14] and Morton[34] also report similar cases. Abrams[1] reports one which was diagnosed mesenteric occlusion and operated. On opening the abdomen not enough pathology was found to warrant surgical intervention. Unfortunately, in this case the condition progressed to infarction and a fatal termination. This emphasizes the border line between medical and surgical treatment.

The writer believes with Connors[8] that occlusion of small branches of the mesenteric vessels are relatively frequent. They cause symptoms of acute abdominal pain and partial obstruction which clear up within a short time. Such a history is not infrequently obtained from old arteriosclerotic individuals. Kaufmann[23] states that in annular infarcts of the terminal mesenteric vessels ileus may develop. In the absence of actual data this must be submitted as a hypothesis only.

All, however, are agreed that when actual gangrene of the bowel occurs the condition is surgical and the mortality 100 per cent if left alone. The difficulty lies in estimating where the dividing line is as evidenced in the case cited above.[1] Operation before demarcation has occurred may be useless because; (1) There may be nothing to see and (2) the extent of the involvement cannot be accurately determined. Progressive involvement after resection would seem to suggest either too early operation or too little resection. The optimum time for operation would be at the time demarcation is complete and before absorption has taken place. Since most cases are not diagnosed, this point is of academic interest only.

The main point is, when possible, to remove all the affected bowel and all the affected mesentery with enough viable tissue to prevent recurrence or progression of the pathology.[33] The type of procedure will vary from either a drainage, or simple exteriorization of the bowel, to resection of the affected part with union of the severed ends. The condition of the patient, the amount and part of the bowel involved and the skill of the operator will determine the technic. A table has been made of cases of living patients compared to the same number of deaths. These cases were picked at random in literature and whenever possible the fatalities were taken from the reports of surgeons submitting recoveries. Thus the question of the ability of the operator is to some extent removed (Table I).

TABLE I

Mesenteric Vascular Occlusion—Comparison Operative Cases

Name	Age	Sex	Amount Bowel Removed	Alive	Dead	Acute	Chronic	Procedure
Frank, Louis [16]	12	M	15 inches		*		*	End-to-end
	10	M	2 feet	*		*		End-to-end
Brady, Leo [4]	48	M	52 inches	*		*		Exterioriz.
	45	F	30 inches	*		*		Lateral anastomosis
	31	F	60 inches		*		*	Side-to-side
	42	F	..	*		*		Side-to-side
	45	F	..		*		*	Side-to-side
	24	F	18 inches	*		*		Side-to-side
Desplas, B. [12]	32	M	60 cm.	*			*	Resected with button
Warnshuis, Fred C. [44]	50	M	2 feet	*		*		Side-to-side
Cowles, Andrew [10]	18	F	3½ feet	*		*		Side-to-side
Loop, Ross G. [27]	35	F	5 feet		*		*	Side-to-side
	29	M	4 feet		*	*		Enterostomy
	56	M	4 feet		*	*		Enterostomy
	35	F	5 feet		*		*	Side-to-side
	47	F	8 feet		*	*		Resection
	46	F	18 inches	*		*		Side-to-side
Bruns [5]	11	M	16 cm.	*		*		End-to-end
Jones and Clark [21]	50	F			*	*		Exploratory
Wulsten, J. [45]	64	M	360 inches	*		*		Side-to-side Anastomosis
Carlson, Guy W. [6]	58	M	5 feet		*		*	End-to-end
Echemendes, Y. [14]	16	F	..	*			*	Exploratory
Gregoire, Ray. [19]	69	M	..		*		*	Exterioriz.
McGuire, S. [31]	27	F	7 feet 4 inches	*			*	End-to-end
	46	F	4 feet 6 inches	*		*		End-to-end
Smith, W. [43]	32	F	15 inches ileum	*		*		Exterioriz. Double barrel stoma.
Sjovall, S. [42]	44	F	90% 450 cm.	*		*		End-to-end
Olivecrona, H. [36]	73	M	3.4 cm.		*	*		End-to-end
Zeno, A. [46]	50	M	4 feet 6 inches		*		*	End-to-end
Reed, Leo B. [37]	50	F	..	*		*		Laparotomy
Jopson, John H. [22]	28	F	6 inches	*		*		Exterioriz.
	50	M	..	*		*		Exploratory
Despard [11]	25	F	..		*		*	Resection
Mason, J. M. [29]	35	F	65 inches	*		*		Resection End-to-end
McCornack, R. L. [28]	40	F	..		*	*		Enterostomy
	40	F	..		*	*		Exploratory
	41	M	17½ cm.	*			*	Exterioriz.

TABLE I (*continued*)

Name	Age	Sex	Amount Bowel Removed	Alive	Dead	Acute	Chronic	Procedure
Green, John R.[18]	42	F	40 cm.	*		*		Resection
Lang, W. H.[25]	60	F	14 inches	*		*		Side-to-side
Rycroft, B. W.[39]	54	M	Entire small intestine		*	*		Exploratory
Morton[43]	55	M	24 inches		*		*	Ileocolostomy
	70	M	30 inches		*		*	End-to-end
	28	M	..	*			*	Enterostomy
Binghamton City Hospital:								
Case 1	67	M	120 cm.		*	*		End-to-end
Case 3	73	F	30 inches		*	*		Exploratory
Case 5	34	M	140 cm.		*	*		Side-to-side
Case 6	42	M	2½ feet		*		*	Enterostomy
Case 8	48	F	39 cm.	*			*	End-to-end

	Dead 24		Alive 24				
	Acute	Chronic	Acute	Chronic			
	12	12	17	7			
Procedure					Total	Dead	Alive
Exploratory	4	..	2	1	7	4	3
Enterostomy	3	3	..	1	7	6	1
Side-to-side	2	4	7	2	15	6	9
End-to-end	2	3	5	2	12	5	7
Exterioriz	1	1	3	..	5	2	3
Exterioriz with Resect.	..	1	..	1	2	1	1
	12	12	17	7	48	24	24

Operated—48 Acute—29 Chronic—19

In the procedures above, enterostomy above the united ends was also done in many cases. Percentages are omitted as misleading and of no value in this small series.

Symptomatology.—Connors[8] states that pain followed by fever and leukocytosis occurs in thrombotic conditions of the heart. He suggests that the same symptoms must occur in thrombotic conditions elsewhere in the body. Meyer[33] reports pain as occurring in each of the 92 cases where intestinal changes occurred. The leukocyte count in 20 of 23 cases where it was taken was above 18,000. "The increase is rapid and occurs very soon after the onset of pain. Only two findings, abdominal pain and high leukocyte count, were constantly associated. The temperature ranged between 96° and 101° F." Connors'[8] statement that some degree of fever and leukocytosis are present

at some stage of the condition seems well taken even in the face of apparent afebrile cases. There certainly would be fever when gangrene occurred.

Aside from the above, the symptoms are inconstant. To quote Meyer[33] again. "Vomiting was present in 55 per cent of the cases and absent in 10 per cent. It occurred after the onset of the pain and was repeated. Nausea was present in only 20 per cent. Blood in the stools was reported in 14 per cent and absent in 8 per cent. Rigidity present in 16 per cent and absent in 15 per cent. Distention at some time in 45 per cent. The findings, except for the high leukocyte count, are essentially the same as those found in early bowel obstruction." We can add nothing to this complete and concise exposition except to emphasize that the pain may be entirely out of proportion to the physical signs.[13] Like coronary thrombosis it may at times disappear only to recurr in more severe form if gangrene occurs. The condition when infarction occurs is really one of intestinal obstruction with the varying signs and symptoms of that condition.

COMMENTS ON TABLE II

Cases 1 and 2.—The presence of mesenteric vascular occlusion due to heart conditions has been emphasized since the early literature. The history of valvular lesions followed later by embolic phenomena elsewhere is known to all. Its occurrence in pregnancy is also fairly common. Report of such cases having normal uneventful pregnancies followed by embolic phenomena later are not so common. Giannone[17] reports a case of mesenteric vascular occlusion very similar to Case 2.

Case 3.—Arteriosclerosis is a common cause of obliteration of mesenteric blood vessels. The appearance of two areas of occlusion at the same time is unusual. Selby[41] reports a case of thrombosis of the mesentery with thrombosis of the vessels of the left foot and left arm. This was in a patient with a fibrillating heart. In Case 3 it is possible that there was a heart condition also, although there was no such history and the heart on entrance showed no apparent abnormality. Another such case is reported by Olivecrona[36] in a male, age 73, with hypertension but with lost compensation. Embolus was the cause of the occlusion.

Cases 4, 5, and 6.—These patients all had operative procedures.

Case 4 had repeated operations and also a question of lues. Either the procedures or the lues might have predisposed to the thrombosis. The pathologist's opinion was that the chronic obstruction had led to stasis in the mesenteric vessels with thrombosis. Referring to the history of chronic constipation of several months' duration Gregoire[19] reports a similar case.

Case 5 shows a thrombosis about a year after operation for an appendix. Cowles[10] reports a case 23 days after uneventful recovery for an acute appendix. Greene and Allen[18] report a case with thrombosis eight months after an appendectomy.

Case 6.—An example of vascular occlusion either coincident or immediately following an acute appendix operation. Meyer [33] reported seven cases

TABLE II

Binghamton City Hospital, 1925–1933

Case Sex Age Date Physician	Onset	Pain	W. B. C.	Vomiting	Temp. Pulse Resp. on admis-sion	Area Involved findings	Procedure	Etiology	Result
Case 1. J. G., M., 67, 62692. 1/26/31. Cunningham, J. J.	Acute 24 hrs. duration	Severe, persistent	13,000 95% Polys.	Severe, persistent	T. 99 P. 98 R. 22	Jejunum, 120 cm. Large amount bloody fluid	End-to-end plus enter-ostomy	Heart	Died in 12 hrs.
Case 2. G. S., F., 30, 34376. 7/29/25. Chittenden, A. S. Marvin, H. B.	Acute 12th day postpartem	Severe, persistent	....	Severe, persistent	T. 98 P. 90 R. 20	Entire sm. bwl., 3 ft. below duo-denum. Large amount bloody fluid	Enteros-tomy	Valvular heart, pregnancy	Died in 24 hrs. Pt. had 2 nor-mal pregnancies previously.
Case 3. V. S., F., 73, 75470. 10/11/32. Griffin, H. P.	Acute 12 hrs. duration	Severe, persistent	....	None	T. 101 P. 92 R. 16	2 ft. jejunum. Mod. amount bloody fluid	Exploratory	Arteriosclerosis	Died in 12 hrs. Pt. also had thrombosis in left axillary artery at same time.

Case 4. G. S., M., 49, 73478. 7/16/33. Allerton, S. M.	Chronic several months duration	Severe, intermittent		Occasional	T. 97.3 P. 76 R. 20	Autopsy. 2½ ft. ileum.	None	Repeated operations	Died
Case 5. W. C., M., 34, 80760. 6/5/33. Behan, W. A.	Acute	Severe, persistent		Severe, persistent	T. 100 P. 100 R. 20	140 cm. ileum term. Large amount bloody fluid	Resect. (lat.) enterostomy	Appendectomy year previous	Died in 48 hrs.
Case 6. I. H., M., 42, 72260. 5/29/32. Sneierson, H.	Acute fol. appendectomy	Severe, persistent	24 hr. af. adm. 13,000	None, mod. persistent af. appen.	T. 98.4 P. 48 R. 16	(1) Acute gangr. retro. appendix. (2) Autop. 2½ ft. patchy necrotic ileum.	(1) Appendectomy. (2) Enterostomy	Appendicitis	Died in 12 hrs. after enterostomy. Mesenteric Thrombosis coincident (?) appendicitis.
Case 7. A. C., M., 50, 59260. 7/15/34. Behan, W. A.	Chromic 2 months, worse 1 week	Severe, persistent	19,700 97% Polys.	Severe, persistent	T. 99 P. 86 R. 26	Autop. Gangr. entire sm. bwl.	None	Thrombo-angiitis obliterans (Buerger's)	Died 36 hrs. after admission
Case 8. W. B., F., 48, 88306. 5/30/34. Sneierson, H.	Chronic 1 week	Intermittent; not severe	9,500 61% Polys.	None	T. 99 P. 100 R. 20	1½ ft ileum, sub-ac. g. blad. Mod. amount bloody fluid	G. B. drain. End-to-end resect. with enteros.	Gall. Blad.	Recovered. Apparent recurrence 16th day spontaneous recovery.

following appendix operations—two of which were associated with acute appendicitis. Morton[34] reported one following an appendix and one found coincident with a ruptured appendix. Case 6 showed a slow pulse of 48. Desplas[12] also reports a patient with a pulse of 48. This may not be pathognomonic but a slow pulse in the face of signs of an acute abdomen in the absence of jaundice is suggestive of vascular insult. It is probable that some of the present appendicitis mortality might be attributed to mesenteric thrombosis.

Case 7.—The occurrence of vascular occlusion in the mesentery in the presence of vascular occlusions elsewhere has been demonstrated. The fact that these occlusions may be due to the same type of pathology has been brought forward by Connors[8] and Averbuck and Silbert.[2] The latter state that there are only nine published cases of autopsy in patients with thrombo-angiitis obliterans and mesenteric vascular occlusion and that only Jager[20] found lesions which he was convinced were true Buerger's disease elsewhere in the body. Because of this, the writer has included the following pathologic report by Dr. V. W. Bergstrom, pathologist, Binghamton City Hospital:

Microscopic Examination, December 20, 1934.—These sections were especially examined for lesions resembling thrombo-angiitis obliterans. "In sections made from the area of mesenteric and bowel necrosis the vessels in general show little pathology except that many of the veins are enormously dilated with blood clot. The walls of one medium-sized vein show a moderate infiltration with polymorphonuclear leukocytes. *Aorta.*—This shows marked sclerosis with large fusiform-shaped areas of fatty infiltration in which are many cholesterol clefts. The intima is very much thickened apparently due to edema and a marked infiltration with wandering cells, mostly large and small round cells, throughout the media, and in some areas there is considerable vascular proliferation in the media. There is remarkably little inflammatory reaction in the adventitia. A medium-size artery, probably mesenteric, shows a marked more recent inflammatory cellular infiltration in all layers but more particularly in the adventitia. Here some of the branches show old fenestrated fibrous thrombi infiltrated with small round cells and masses of old blood pigment. No giant cells were noted. The internal elastic membrane of this vessel is intact throughout the section. A medium-sized vein in the same area shows a moderate amount of small round cell infiltration in the walls but no thrombosis. *Liver.*—There is a generalized chronic inflammatory process around the hepatic trinity obviously involving the veins and arteries. A large hepatic vein not associated with artery or bile duct shows considerable intramural small round cell inflammation. *Heart, Pancreas and Lungs.*—The vessels show no inflammatory reaction.

From these findings it would appear that in this case there is no generalized inflammatory condition of the arteries and veins, but that a condition resembling somewhat that described by Buerger existed in the region of the mesenteric artery, and in my opinion was the cause of the thrombosis.

Doctor Bergstrom has another case, as yet unpublished, which shows the same vascular changes all over the body. There were no thrombosed areas in this patient. Zeno[46] and Brady[4] have also reported cases of mesenteric occlusion occurring in patients with Raynaud's disease.

Case 8.—Mesenteric occlusion following gallbladder disease is fairly common.[33] The writer is not sure whether the condition in this case was following an acute gallbladder attack or whether it was entirely a vascular affair.

It would seem as if this was a good example of a patient seen when the infarcted area was completely demarcated, but with no absorption symptoms. Medical treatment in the face of apparent progression of the thrombosis during convalescence was successful in this case.

General Résumé Cases in TABLE II.—The general signs and symptoms corresponded fairly accurately to the case reports in literature. Pain often out of proportion to the clinical signs was noted in each case. Fever and leukocytosis were present in most cases. Abdominal signs varied from none to marked rigidity. Vomiting was present in most cases, but contrary to what one would expect it was entirely absent in Case 3, in which there was gangrene of two and one-half feet of bowel. The diagnosis was made in only one case and thrombosis elsewhere suggested the true condition (Case 3). Procedures used corresponded to those reported by other writers.

Diagnosis.—The diagnosis of mesenteric vascular occlusion is rarely made. This is due to the type of pathology which may cause symptoms varying from a mild distress to a severe shock-like state resembling an acute hemorrhagic pancreatitis. Because of this fact, and the fact that detailed discussions have appeared in literature, the subject is only briefly discussed.

Mesenteric thrombosis for diagnostic purposes may be divided into two classes—Medical and Surgical. These may be subdivided into acute and chronic types with their border-line cases.

Medical Thrombosis.—By this is meant small occlusions insufficient to cause intestinal gangrene or slow occlusions in which compensatory circulation occurs. This group would include the intermittent claudication of the abdomen of Meyer.[33]

Symptoms.—The only constant symptom is pain. Intestinal symptoms if present would be confined to signs of partial obstruction which gradually cleared up. Surgical intervention is useless and contraindicated in this condition. Medical thrombosis is probably almost never diagnosed and no pathologic data have been found to substantiate this entity according to Connors.[8]

Surgical Thrombosis.—By this is meant sufficient infarction to cause gangrene of some part of the bowel. The pathology in this case, whether acute or chonic, is exactly the same. The symptoms would correspond with variations according to the type and amount of occlusion. Pain out of proportion to the clinical signs is usual. Fever, leukocytosis and vomiting follow pain and in turn are followed by signs of intestinal obstruction, peritonitis and death if surgical intervention is withheld. The above may occur within a few hours or may take a long time. The condition often shows very few symptoms until gangrene takes place (Case 8). In the presence of vascular disease or signs of thrombosis elsewhere the diagnosis may be made. At other times the writer feels that the diagnosis of mesenteric occlusion could correctly only be mentioned as one of the possible causes of the condition.

The border-line between Medical and Surgical occlusions is obscure. In cases where laparotomy alone was done and the patient survived, the condition

was Medical. In the state of our present knowledge of the condition, a diagnosis of intestinal obstruction with the possibility of occlusion would seem to answer the purpose practically. Since intestinal obstruction, under which mesenteric occlusions are classified, and of which they are a very small part, is difficult to diagnose because of its manifold variations as evidenced by a mortality which is reported to be from 40[32] to 60 per cent,[44] the diagnostic problem is self-explanatory. The differential diagnosis would, according to this idea, be between the conditions simulating intestinal obstruction, and has been repeatedly brought out.

SUMMARY

(1) Mesenteric vascular occlusion is of much more frequent occurrence than is generally supposed. Occlusions sufficient to cause intestinal infarction are however uncommon, but are not so rare as literature would indicate. A brief résumé of recent literature has been recorded and the chief points noted have been emphasized in the case reports. The writer agrees with Connors[8] in his hypothesis of occlusions elsewhere in the body resembling coronary occlusions. In literature and in personal experiences the symptom complex of pain out of proportion to the objective signs, fever and leukocytosis have been demonstrated. Since slight coronary occlusions are frequently passed off as mild indigestion and at the time clear up without further signs or symptoms, it seems logical that the same condition may occur in the mesentery. Mesenteric occlusions which were found at autopsy for other causes as in Chiene's case would tend to support this view.

(2) Report of a patient with thrombo-angiitis obliterans who died with mesenteric vascular occlusion is added to the literature.

(3) Another living case is reported.

(4) The diagnosis of mesenteric thrombosis is rarely made. A diagnosis of intestinal obstruction would seem to be sufficient for practical purposes. When such symptoms occur and persist, operative interference is indicated.

(5) The mortality would seem to depend upon the time when operated. If the part is removed before too severe systemic reaction has taken place, the patient stands a good chance of recovery regardless of the procedure used. Resection whenever possible would seem to be that most commonly employed.

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PERFORATED ULCERS OF THE DUODENUM

A STUDY OF FORTY-ONE CASES

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THE writer presented in 1921[1] and 1927[2] 15 and 27 cases, respectively, of acute perforation of ulcers of the duodenum. Simple closure of the perforation by inversion, with or without omental reinforcement, was advocated as the procedure of choice. A concomitant posterior gastrojejunostomy seemed indicated in but a small minority of cases. To the above series, 14 additional personal cases are added, thus comprising a group of 41 consecutive cases operated upon between October, 1912, and December, 1933. All were cases of duodenal perforation and prepyloric lesions are excluded.

The first successful operation for acute duodenal perforation was reported by Heussner in 1892, although Mikulicz had advocated simple closure in 1880. For many years simple inversion closure was the technic of election. Although a majority of the postoperative cases remained well and asymptomatic, a definite group had symptoms of greater or lesser severity. Some developed real stenosis and were relieved by gastro-enterostomy. In some clinics, notably Deaver's,[3] a primary gastrojejunostomy was advocated in all cases but still the end-results in certain instances were unsatisfactory. Primary pyloroplasties of Heineke-Mikulicz, Horsley and Finney[4] were advised by others. Again a group remained "uncured." Latterly, due to the European influence of radical tendencies in gastric surgery, as taught by Finsterer, Von Eiselsberg and others, primary pylorectomy, partial and even subtotal gastrectomy is recommended in the early hours of perforation.

Acute duodenal perforation from ulcer is a relatively common pathology and, after 40 years of surgical therapy, it seems remarkable that such divergent opinions exist among the leaders of the profession. All agree that the time element is of first importance. The vast majority of cases recover if operated upon within the first 12 hours by simple inversion closure. The great question is whether perforated ulcers are cured by simple closure, will the patients remain well and asymptomatic, or is more radical surgery primarily indicated? This study concerns itself with a fair evaluation of all the facts in an endeavor to reach an unbiased opinion as to what operative procedure seems to offer the best, not only immediate, but end-results.

Anatomy and Physiology.—A few anatomic relations and physiologic functions are worthy of review. The cardiac orifice and the first part of the duodenum are fixed parts of the stomach. When empty the stomach lies transversely in the upper abdomen; but when filled it assumes a vertical shape, which is due to the descent of the prepyloric part. In accord with gravity therefore, the weight bearing part of the viscus is in the distal part of

the pylorus and that part of the duodenum adjacent thereto. This pendent portion of the stomach, which includes the pylorus, the first part of the duodenum, and the distal part of the lesser curvature, has a blood supply that is considerably less than the stomach proper. Also, in addition to this subvascularization, the mucosa is here intimately attached to the muscle layers, forming rugae.

These peculiarities of anatomic detail allow very little dilatation or contraction and the consequent rigidity predisposes more or less to traction anemia. The anemia peculiar to this locale lasts about two hours after eating and may be regarded as a potent predisposing factor for selective embolic infections, thrombosis or tissue digestion. This anemia also influences the healing of ulcers occurring in this area subsequent to operative interference.

In the process of digestion, when food enters the stomach, it becomes liquefied and mixed with the gastric juice and the sphincter at the pyloric extremity does not relax until chymification is complete. The balance between the motile powers of the stomach, as shown by the retention of its contents and their later propulsion through the orifice of pylorus, is properly maintained. These motile powers are probably segmental in each curvature.

This motility mechanism, however, is badly deranged by gastro-enterostomy. Normally the acidic chyme, when it flows into the duodenum, transforms the prosecretin into secretin and thus establishes pancreatic secretion. The churning movement of the duodenum intimately mixes the chymified food with the bile and pancreatic ferment and then passes it into the jejunum. Gastro-enterostomized patients are subject to a change that may be termed revolutionary in so far as the physiology of their digestion is concerned. Gastric contents that are improperly prepared enter the jejunum, which in consequence must do the work of the duodenum, a part of the process of digestion for which it has no physiologic fitness. The subjective and objective sequences of this digestive dysfunction may be pain, vomiting, diarrhea—in fact, the whole gamut of dyspeptic signs and symptoms. That many of the patients thrive despite this handicap only shows the adaptability of the human economy. It is nevertheless true that gastro-enterostomy performed for the purpose of relieving scar tissue obstructing the pyloroduodenal orifice is, in the majority of cases, an entirely satisfactory procedure. In such cases of obstruction there has existed for some time an altered function, both motile and secretory, mostly of the stomach, to a lesser degree of the duodenum. For that reason, one chooses the lesser of two evils and makes a short circuit, trusting to Nature's well known tendency to establish a satisfactory balance. Conversely, it is well known that in the absence of true pyloroduodenal stenosis, gastrojejunostomy is often fraught with future disaster. For several months the patient is likely to be comparatively free from symptoms, but later results may be most disappointing.

The cardinal indication, therefore, for gastrojejunostomy would be actual or organic stenosis. This form of stenosis did not obtain in the majority of the cases cited here, and from discussion with colleagues, the impression

would seem to prevail that in relatively few perforations from duodenal ulcer does real stenosis occur. Moreover, it must be remembered that Nature overcomes many apparent stenoses. This fact is well demonstrated in four cases, which were subsequently operated upon for (*a*) incisional hernia; (*b*) acute suppurative cholecystitis; (*c*) gastrojejuno-colic fistula and (*d*) subphrenic abscess. The duodenum in all four cases was restored to normal yet apparent stenoses presented at the time of perforation and in one case it was so pronounced that a primary gastrojejunostomy was added. The evidence in these four cases is convincing testimony of how completely restored to normal the diseased duodenum may become. Not only was there no evidence of scarring, but practically none of adhesions.

There are numerous cases in the literature in which subsequent exploration for other pathologies revealed that there was no trace of the old ulcer (Basset,[5] Pannett,[6] Lecene). There is ample experimental evidence to indicate that pyloric stenosis does not occur as commonly as supposed. Stewart and Barber[7] performed cautery puncture of the duodenum in dogs and infolded the opening so as to practically occlude its lumen. Even this did not produce stenosis clinically or by roentgenologic studies. Eliot,[8] in 1912, experimenting on cats, found that the constriction produced by excising two-thirds of the circumference of the duodenum failed to produce stenosis. Experimentally it is difficult to thus produce true stenosis. The writer is of the impression that should the diameter of the duodenum be reduced not more than one-half, due to the infolding of the perforation, no stenosis will obtain.

Pathology.—A better appreciation of the pathologic varieties of ulcer may help to crystallize the surgical therapy. Of the well established, easily demonstrable chronic ulcer we have ample knowledge; of the so called acute ulcer, the erosion, the ulcerating lesions which recover and disappear under medical treatment, our knowledge is meager. It is highly probable that from time to time small defects occur in the gastric and duodenal mucosa, with or without symptoms, and that these spontaneously disappear. Defects of greater magnitude, true ulcers with typical clinical findings, sometimes completely disappear under medical treatment. The so called remissions and exacerbations in these histories may be explained upon the ground of recurring new ulcers. Once the lesion has become a well established indurated type the pathologic process is prone to become progressive with little or no remission of symptoms. These true surgical ulcers present five general types:

(1) The large ulcer with much scar tissue formation encroaching upon the lumen of the duodenum and accompanied with more or less extensive extrinsic adhesions.

(2) The medium sized ulcer with moderate scar tissue infiltration, without narrowing of the lumen.

(3) The small ulcer with a nonindurated or only slightly indurated base.

(4) The acute necrotic ulcer.

(5) Multiple ulcers, including the so called "kissing" type.

Perforation may occur in any of these, and as the pathology is varied so

also are the indications for surgical repair. To dogmatically state that suture with posterior gastro-enterostomy should be employed in every instance is as illogical as to assert that simple closure will always suffice. Good surgery aims to cure the patient with the least insult to anatomic and physiologic function.

Clinically most acute duodenal perforations are those of Types 2, 3 and 4. There is a remarkable monotony of appearance to these lesions. They are simple, single, round, slightly indurated, 1 to 2 cm. in diameter, on the suprapapillary part of the duodenum (the proportion is 450 to 1) and nearly always in the first one and one-half inches of the anterior and superior surface. Those occurring at the junction of the pylorus and duodenum are probably for the most part duodenal. In these the pyloric veins are often obliterated. Much less than half of those ulcers present adhesions to neighboring structures; the gallbladder, liver, colon, stomach and omentum. Most ulcers that perforate suddenly are nonadherent to adjacent viscera, and when adhesions are present in such they may be of recent origin. Disease of the appendix and gallbladder is a frequent concomitant.

The perforation is usually from 2 to 5 Mm. in diameter, a typically punched out hole in the crater of the ulcer. If carefully examined it will be noted that the entire ulcerating portion is extruded as the result of embolism or thrombosis. The remaining peripheral induration is the protective zone that accounts for the rapid healing of the lesion after closure. The writer believes that in many cases this induration is soon absorbed and the duodenum is restored to its normal condition without any macroscopic evidence of previous disease. Thus one seems justified in stating that lesions of Types 2, 3 and 4, which form the majority of duodenal perforations, are best treated by simple closure. Similar good and lasting results obtain by cautery puncture and simple closure in nonperforated ulcers of this type. The perforation or blowout replaces the cautery.

The large ulcer, with an abundance of scar tissue induration which encroaches upon the lumen of the duodenum and which usually is adherent to neighboring organs, presents a different pathology and demands appropriate surgical therapy. Such lesions, prior to perforation, have produced a partial stenosis thereby resulting in a change in the motile and secretory functions of the stomach. The closure of these ulcers after perforation usually produces a real rather than an apparent obstruction. Consequently they present the cardinal indications for gastro-enterostomy, namely, stenosis plus a preexisting altered gastric function (pyloroplasty of the Finney and Horsley type has not proved efficacious in the therapy of these types). Furthermore, simple closure in this type seldom results in permanent cure, and the relapses after such a closure have helped to popularize primary gastro-enterostomy for all types. The treatment of the multiple ulcer type must be governed by the pathologic problem at hand.

From the above mentioned pathology, it will be noted that for practical purposes perforated ulcers of the duodenum resolve themselves into one of

two types. First, the soft lesions—the more common type—characterized (*a*) by their relatively smaller size, (*b*) by their superficial extent, (*c*) by their failure to penetrate deeply prior to the embolic or thrombotic phenomenon which results in perforation, (*d*) by the absence of dense induration, and (*e*) by lack of adhesions and encroachment upon neighboring structures. Second, the calloused type, characterized (*a*) by their large size, (*b*) by their deep penetration, (*c*) by their dense induration, (*d*) by their firm adhesions to neighboring structures, and (*e*) by their tendency to produce mechanical complications. It is the opinion of the writer that simple closure by inversion with fine chromic catgut will cure the vast majority of the first group, whereas the calloused types require in addition a primary gastro-enterostomy, or perhaps some form of pyloroplasty. The successes and failures in this series are in accord with these general principles.

Diagnosis.—The diagnosis of acute perforation can be easily made in most cases. The anamnesis of previous indigestions, often a recent exacerbation with preperforation pain of several days due to serosal involvement, the suddenness of onset, the agonizing pain, constant in character in contradistinction to the colic-like pain of appendicitis, cholecystitis, intestinal obstruction or renal colic, the vast extent and the degree of rigidity and tenderness so soon after onset, the comparatively slow pulse, slight or no febrile reaction is a familiar picture. A few points are worthy of emphasis: vomiting occurred in less than half of the cases in this series (17 cases). Rectal examination may elicit extreme tenderness soon after perforation, much earlier than in appendicitis. The symptom of shock has been overemphasized. In this series but nine were in any degree of shock. Apparently shock, when present, occurs soon after perforation and is transitory. It should also be mentioned that in stout individuals there is only moderate rigidity. Also in the transitional period passing on to true peritonitis, there is a free interval when the pain is ameliorated. One patient seen 18 hours after perforation sat up in bed exclaiming, "He felt quite well." No opiate had been administered. His abdominal cavity contained the usual amount of duodenal contents and the peritoneum was markedly injected. More than half of the cases show obliteration of liver dulness either partial or complete. It is merely a corroborative sign and is in no wise pathognomonic. The left shoulder pain, mentioned by Gibson,[9, 10] as occasionally occurring early after perforation, occurred in three cases and is probably a pneumogastric-spinal accessory reflex rather than pain of peritoneal or anginal origin. The subdiaphragmatic gas bubble, seen in vertical roentgen ray plates, is an early diagnostic help. It is especially helpful in cases of small perforations with atypical signs. Occasionally a localized zone of tympany just below the xiphoid obtains early.

In the preperforative irritation stage, physical examination may reveal acute tenderness over the ulcer with some rigidity of the overlying muscles. This connotes a deep ulcer with peritoneal irritation and should be an indicaton for surgical intervention. (Case VII well illustrates this danger signal: Thus a female of 57 years for six months had typical hunger pains occurring

three hours after eating. Her examination elicited acute tenderness over the site of the pylorus and moderate rigidity of the rectus. Temperature, pulse and blood count were normal. She was put to bed and placed upon Lenhartz diet. Tenderness and muscular spasm persisted. On the eleventh day of treatment perforation occurred suddenly while she was at absolute rest.)

Treatment.—The treatment of acute perforation is immediate operation regardless of any degree of shock that may be present—as the patient's condition rapidly improves with the relief of intraperitoneal tension. A four-inch right median rectus incision is deepened down to the peritoneum. A point of practical importance is to determine the lower border of the liver. This should limit the upper angle of the incision. If a small nick is first made into the peritoneum, a little free fluid will well up into the incision, and gas bubbles erupting through this will clinch the diagnosis of perforation. The escaped contents are best aspirated, especial attention being paid to Morrison's space, the right lumbar gutter, and to the toilet of the pelvis. With moist pads the surrounding structures are gently pushed aside and the perforation sought. Fibrin deposits are an excellent guide to the point of perforation and not infrequently gas bubbles point out the way. If the perforation is obscure, slight pressure on the stomach may cause bubbles to appear. Closure of the perforation is accomplished by infolding the ulcer with fine chromic catgut reinforced occasionally with an omental tab. The expediency of a primary gastrojejunostomy is determined by the pathology. If simple closure is performed, one tests the patency of the lumen of the gut. If the tip of the little finger can be insinuated through the site of closure, there is little danger of obstruction. One then makes a search for secondary ulcers, gallbladder and appendiceal disease.

The added risk of primary gastro-enterostomy, before the advent of peritonitis, is slight in a patient whose condition during operation, as regards respiration, aeration, and circulation is good. The danger of working in a potentially infected field is more theoretical than real. The real dangers are two-fold: (1) a 2 to 3 per cent chance of future gastrojejunal ulcer formation, and (2) the late secondary sequelae which occur in some cases despite perfect technic in the hands of the most skilful. Therefore, unless the pathology is such as to demand a primary gastro-enterostomy, *i.e.*, definite obstruction, simple closure should be performed. A good practical rule is, when in doubt, do not perform a gastro-enterostomy. It can be performed later, if necessary.

If a careful peritoneal toilet be made by aspiration, there is no need of drainage except of the mural tissues. The suprapubic stab wound seldom drains, but may produce adhesions and is contra-indicated. Drainage to the site of closure is never instituted as several duodenal fistulae have resulted thereby. The slow perforations with abscess formation are best treated by simple incision and drainage. If a fistula ensues, a secondary closure with gastro-enterostomy is indicated.

Following operation the patient is placed in a semirecumbent position, given one or two doses of morphine and a 5 per cent glucose rectal drip.

Small amounts of water by mouth are permitted after four hours. On the third day, a modified Sippy diet is instituted and adhered to for its entire course. At this time, the foot of the bed is kept elevated about six inches. This is thought to relieve traction anemia upon the pyloroduodenal segment. Frequently small amounts of alkalies are administered the first two weeks. The patient is then given a light, selected, nonbulky diet with crackers and milk between meals for the next two weeks. At the end of two months, a roentgenologic examination is made. The patient is warned of the dangers of dietary indiscretions and receives medical supervision for at least six months.

The series is comprised of consecutive personal cases operated upon between October, 1912, and December, 1933. There were 39 males and two females. Although duodenal ulcers are more common in males, the relative incidence in the two sexes does not account for only 3 to 5 per cent of perforation in women. Many suppositions have been offered. White[11] well answers them by stating that he cannot become enthusiastic over any of these "attempts at the explanation of a very puzzling fact." The youngest patient was 21 years; the oldest 57; the average 36 years. Most large statistics reveal above 40 per cent in the fourth decade. However, there are reported cases occurring in young children and also in the aged. It is interesting to note that no case was obese (*versus* gallbladder type) and that several had been under severe mental or physical strain. Their occupations were varied and irrelevant. Twenty-seven (66 per cent) gave a typical previous ulcer history varying from a few months to 11 years. Eleven (26 per cent) presented indefinite dyspepsia symptoms. In two cases there were no symptoms to the moment of perforation. In these ulcers the evidences of inflammation and repair were absent and the picture was one of focal necrosis. Both have remained asymptomatic following simple inversion closure.

Four cases gave a history of melena, none of hematemesis. In Deaver's series of 55 cases, blood was found only twice in the stools or vomitus. In White's Roosevelt Hospital series of 62 cases only 3 per cent had bleeding. It is well recognized that bleeding ulcers seldom perforate.

Only three cases perforated within the first year of symptoms and the average duration of symptoms until perforation was 46 months. The incidence of chronic ulcers which perforate appears very small and the danger very slight.

Of the 41 perforations, 37 were acute and four slow perforations. Of the slow perforations, one presented a large abscess extending from the liver to the iliac crest. This was of two weeks' duration. Another case perforated slowly and remained localized. The third case ruptured into the lesser sac, presenting the clinical picture of biliary obstruction with jaundice. The fourth occurred in a penitentiary inmate who was under treatment for drug addiction. At first the patient received little attention as his epigastric pain was thought to be due to drug withdrawal. The writer saw him on the second day, at which time he was walking about the ward complaining of epigastric, and especially mid-lumbar pain. The abdomen was negative. Two days later

he developed upper right rectus rigidity. Temperature, pulse and leukocyte count were normal. A vertical roentgen ray examination showed a subdiaphragmatic bubble. Laparotomy failed to reveal any pathology. The lesser sac was opened and found normal. For three days the patient remained quite comfortable. Following another attack of severe pain the patient went into partial collapse and died 40 hours later with a temperature of 105.4°. The upper abdomen was moderately distended but not definitely rigid. Autopsy revealed turbid fluid in the lesser sac and a sloughing 2 cm. ulcer on the posterior wall of the duodenum at the papillary level. Fortunately ulcers in this silent area are rare.

Of the acute perforations (37) the shortest time elapsed until operation was three hours, the longest 26 hours, the average being 10 hours plus. The temperatures averaged 99.6° per rectum, pulse 86, respiration 23. White blood cells 15,400 with 82 per cent polymorphonuclears. Cultures taken in 21 cases were all sterile, which is usual during the first 12 hours following perforation and many are sterile the first 18 hours. Of the 37 cases a correct preoperative diagnosis was made in 34. Two were mistaken for perforative appendicitis and one for acute hemorrhagic pancreatitis because of the pronounced shock, persistent vomiting and only slight epigastric rigidity.

In this series simple closure was performed in 32 cases and concomitant gastrojejunostomy in eight cases. One case, simple closure, died suddenly on the fifth day (possibly of embolism). The other death occurred in the patient explored for what apparently was a perforating ulcer, thus giving an operative mortality of 5 per cent.

One patient in whom a transverse incision was employed (1919) returned in three months suffering from an incisional hernia. During repair, the duodenum was carefully searched for the old ulcer site, it had been a soft ulcer type of one year's duration. The duodenum appeared normal. Another developed an acute suppurative cholecystitis four months postoperative, requiring cholecystectomy. The duodenum was free of adhesions and the ulcer site had disappeared.

A third case upon whom a primary gastrojejunostomy was performed, also cholecystectomy and appendectomy, remained well for four and one-half years. He then developed a gastrojejuno-colic fistula wtih the classical syndrome of left epigastric pain radiating to the left groin. At operation there presented a gastrojejunal-colic fistula about 2 cm. in diameter. The remarkable feature was the almost negligible pathology at the former duodenal ulcer site. There was no scarring, no induration, no stenosis and few adhesions. The procedure consisted in undoing the gastro-enterostomy, closing the gastric and colic atria and resecting three inches of the jejunum with lateral anastomosis. The patient was discharged on the sixteenth day and has remained asymptomatic.

A fourth case, operated upon 13 hours after perforation, developed a subphrenic abscess. Upon reoperation 27 days later the duodenum was restored to normal.

These four cases are highly presumptive evidence that perforation tends to cure the ulcers and that the duodenum is capable of complete restitution to normal, even though apparent stenosis obtains after closure. Twenty-four patients have been followed from one to 20 years. Of these, 18 had simple closure and six concomitant gastro-enterostomies. Of the 18 simple closures 14 (78 per cent) have remained well and asymptomatic. One required a secondary gastrojejunostomy two years later for hemorrhage and remained well thereafter. Three have digestive upsets unless a careful diet is followed. In all three the gastro-intestinal series are negative. Of the six gastro-enterostomized patients, who have been followed, only three are quite well (50 per cent). One required a secondary operation for intestinal obstruction from bands about the appendicectomy site, one had the gastrojejunostomy undone for gastrojejuno-colic fistula and the third is generally miserable with dragging epigastric pain and occasional diarrheal attacks.

In conclusion one seems justified in emphasizing the importance of reporting the end-results of the treatment of perforated ulcers of the stomach and duodenum as separate entities. The immediate results depend chiefly upon the time interval that has elapsed after perforation. Only by careful follow-up records extending over long periods can reliable statistics be obtained as to ultimate cures. Undoubtedly the duodenum is capable of complete restitution to normal even though apparent or mild degree of real stenosis obtains after closure. The end-results of simple closure in this series are much superior to those treated by gastrojejunostomy. Simple closure is the operation of choice of most surgeons.

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ENLARGEMENT OF THE GALLBLADDER

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The normal gallbladder shadow has not been defined, nor has much attention been directed to the size and contour of this organ as shown by the roentgen ray after the administration of the dye. Before the advent of the dye method of depicting the gallbladder, everyone was concerned with the presence or absence of stone showing in the radiograph, and it naturally followed that the presence of stones was the most significant finding with the new method. Added to this, the filling and emptying of the gallbladder with the dye gradually took on significance as experience increased with this new method. During a four year study of patients with gallbladder disease at the New York Post Graduate Hospital, the combined Medical and Surgical Clinic has gradually come to realize the importance of changes in the size and contour of this organ.

In patients with typical gallbladder symptoms, definite pathology was found to be present and borne out by operative findings even though the radiograph showed repeatedly the absence of positive or negative shadows of stones and normal filling and emptying. The most important change is enlargement, for in enlargement one has a definite result of stasis, the most frequent accompaniment of gallstones found in operative specimens.

Enlargement of the gallbladder, as shown by roentgen ray shadows and in operative specimens, follows, in the main, an hypotonic and an hypertonic type. In the former, a rounded ballooon type of shadow appears (Fig. 1, *a* and *b*), which, when removed, distended and dried, appears as in Fig. 2.

The latter types are elongated, tubular and pear shaped, with convolutions in ampulla and cystic duct (Fig. 3, *a* and *b*), and when removed and prepared are represented in Fig. 4.

The hypotonic type of gallbladder shadow is found in those individuals having few symptoms ascribable to the organ directly, but with the usual type of dyspepsia associated with the achylia, overweight and indolence of middle age.

The basic cause resulting in such a change in the gallbladder can be ascribed to dilatation due to the normal secretory pressure of bile in the presence of atrophy and atony in the wall of the viscus, such as is shown in specimens removed at operation.

Dilatation such as this should be harmless and produce no symptoms, were it not for the resulting stasis that is particularly important during periods of child bearing or rapid loss of weight, when the cholesterol of the bile increases and stasis of bile may result in the formation of the so-called

metabolic single cholesterol stone (Fig. 5). Such dilatation of the gallbladder as this, with or without stone, is most often found during a routine physical examination in a gouty or rheumatic individual, frequently when looking for a focus of infection in the patient with osteoarthritis. We may say here that

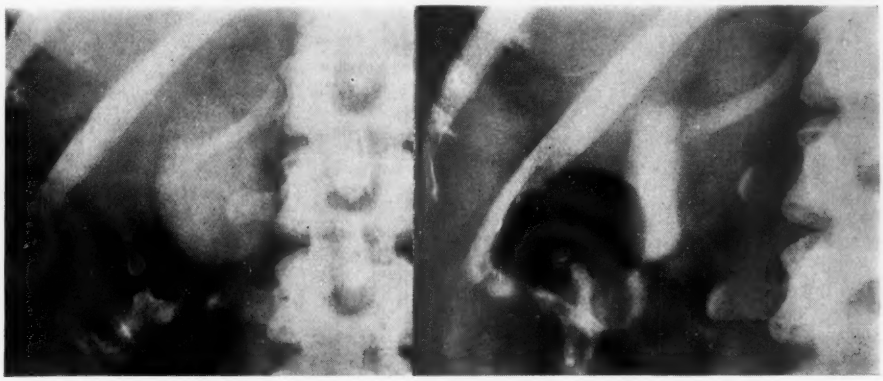

FIG. 1a. FIG. 1b.
Enlargement of the hypotonic type gallbladder, as shown radiographically.

in none of these types of patients have we found such a gallbladder to be important as a source of infection.

The surgical importance of such a gallbladder without stones does not arise, and this type of organ deserves surgical consideration only in the presence of stone. Before impaction of the stone in the ampulla surgical removal prevents this accident, which results in hydrops in the absence of infection,

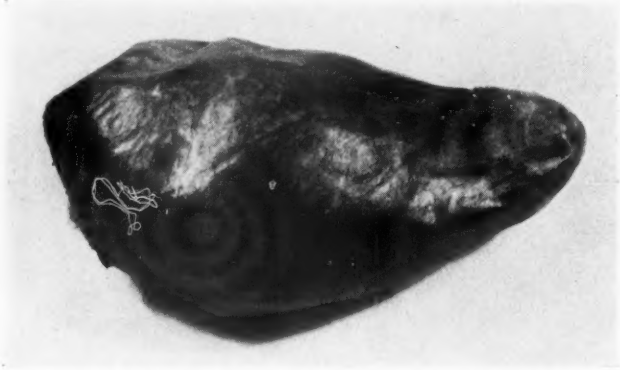

FIG. 2.—An hypotonic type of gallbladder distended and dried.

and acute infectious gangrene and abscess in the presence of infection or pressure necrosis of the viscus.

From a purely surgical standpoint, the evolution and final stage of this gallbladder is shown in Figs. 6, 7, 8, 9, 10 and 11.

Fig. 6 shows a balloon type of gallbladder, thin atrophic walls, short straight cystic duct, promoting stasis.

Fig. 7.—An early impaction of a pure white cholesterol stone in a mod-

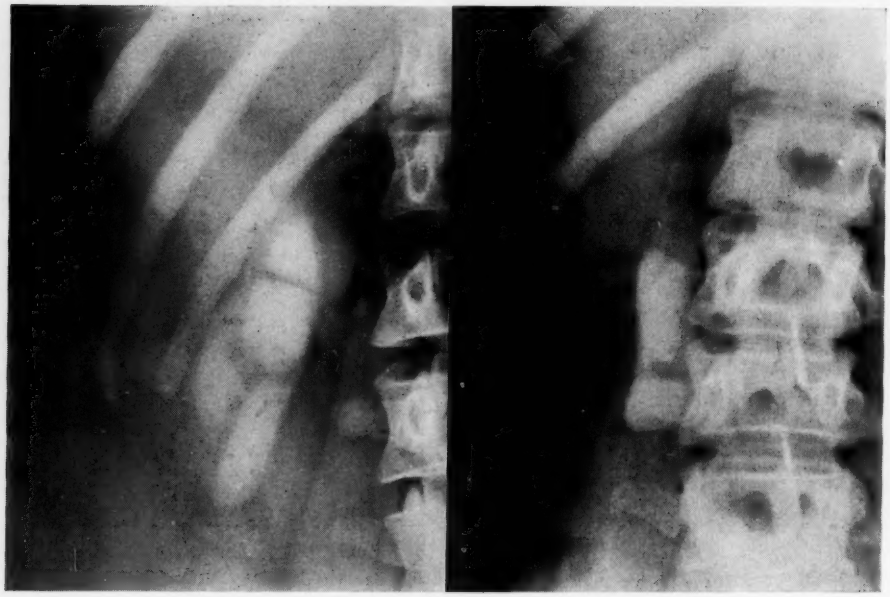

FIG. 3a. FIG. 3b.
Hypertonic type of gallbladder as shown radiographically.

FIG. 4.—A hypertonic type of gallbladder removed and prepared.

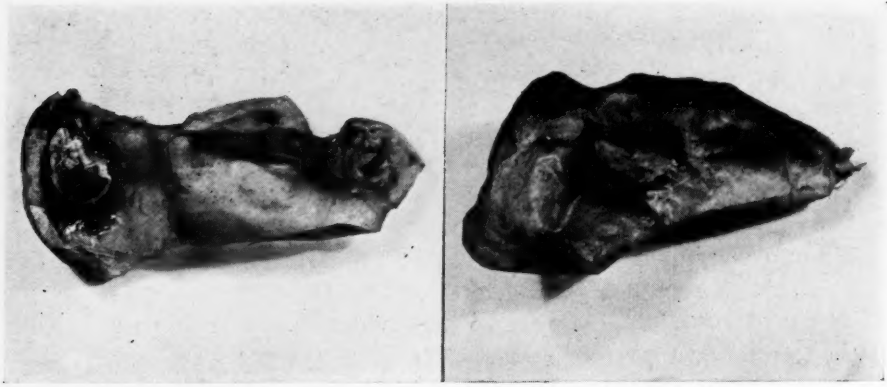

FIG. 5.—Dilation of the gallbladder.

FIG. 6.—Balloon type of gallbladder.

erately enlarged gallbladder with hydrops. The walls were edematous, not acutely inflamed and not infected. This specimen was removed at the first attack of impaction.

FIG. 7.—Impacted cholesterol stone. Edematous gallbladder.

FIG. 8.—Pigment incrusted stone. Inflamed gallbladder.

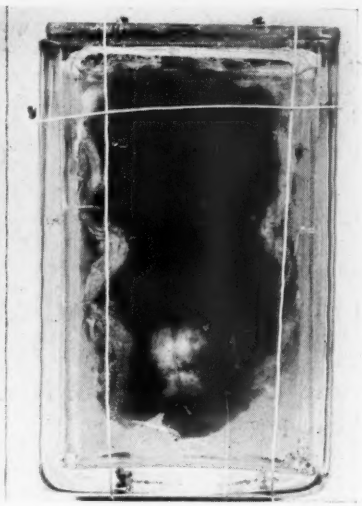

FIG. 9.—Enlarging stone. Fibrosis of gallbladder.

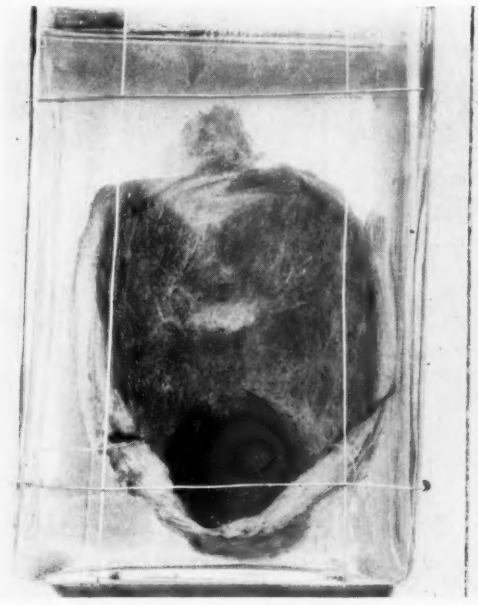

FIG. 10.—Enlarging stone. Fibrosis of mucous membrane.

FIG. 11.—Contracture about stone.

Fig. 8.—The gallbladder was larger, the cholesterol stone was discolored, the walls were edematous, inflamed and infected. This specimen was removed during the subsequent attacks of impaction and infection.

Fig. 9.—The gallbladder was large and round, the stone larger and more discolored, its wall was thickened, fibrotic, inflamed and infected. This speci-

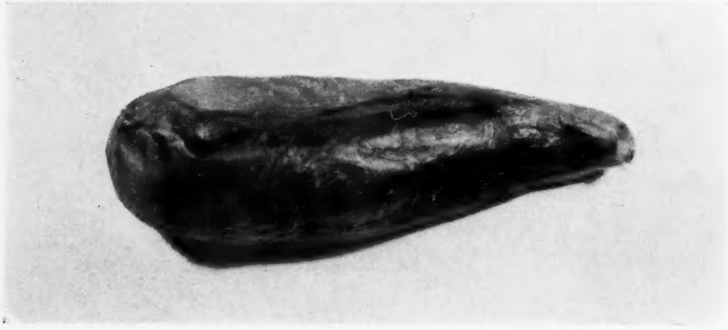

FIG. 12.—Moderately enlarged, tubular, pear shaped, with no convolutions of the ampulla and cystic duct around the cystic artery and vein. The walls are moderately thickened.

men showed the effects of former attacks of impaction and infection, as well as the present one.

FIG. 13.—A similar enlargement with multiple pigment, calcium, cholesterol stones.

Fig. 10.—A large round gallbladder, containing a large pigment encrusted cholesterol stone. Its wall showed mainly fibrosis and thickening from chronic

FIG. 14.—Similar enlargement, similar multiple stones with impaction of a stone in the cystic duct between the valves of Heister. The cystic duct is further curved back upon the ampulla.

impaction of the stone with low grade infection leading to a purulent hydrops of long standing. Operation after acute symptoms had subsided.

Fig. 11.—The final stage. The gallbladder is small, round and contracted down to fit a large pigment encrusted cholesterol stone. Its wall was very thick and fibrous. There was little or no detritus present and the stone is finally encysted, resembling an alligator pear; the meat, the gallbladder wall, and the pit, the stone.

The hypertonic type of gallbladder shadow (Fig. 3) is found in those indi-

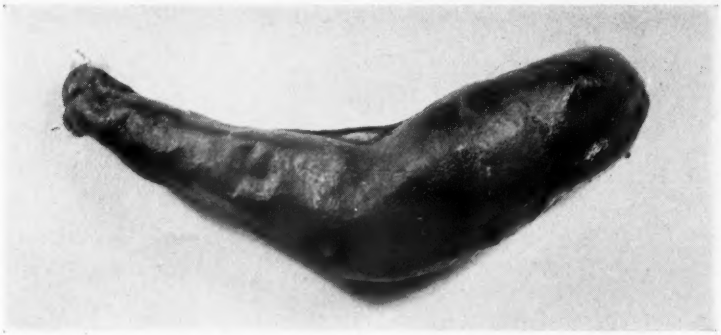

FIG. 15.—Further enlargement and hypertrophy, more acutely convoluted cystic duct and ampulla (the vessels do not seem to elongate as the cystic duct and ampulla do, thereby necessitating a ruffling of this region) as the attacks of impaction and increased pressure continue.

viduals having marked symptoms of pain, attacks of colic, frequently requiring sedatives long before stones can be demonstrated either by roentgen ray or in operative specimens, accompanied by the usual type of dyspepsia associated with hyperacidity, plyorospasm and duodenitis.

The basic cause resulting in such change in the gallbladder can be ascribed to enlargement due to an increase in pressure within a resisting gallbladder

FIG. 16.—The cystic duct and ampulla have curved back to accommodate the length of the cystic vessels.

wall. In the presence of hyperacidity, pylorospasms, duodenitis and spasm of the sphincter of Oddi, there should be brought to bear upon the gallbladder the full secretory pressure of the liver. Under such conditions, the viscus of normal tone should enlarge, hypertrophy, and retain its normal contour, even though exaggerated.

Dilatation, such as this, should produce symptoms of pain and colic, as has

been found to be the case, and stasis resulting in stone formation of a different type. Many families of pigment cholesterol stones are usually found in gallbladders of this type of long standing. Such gallbladders are usually found

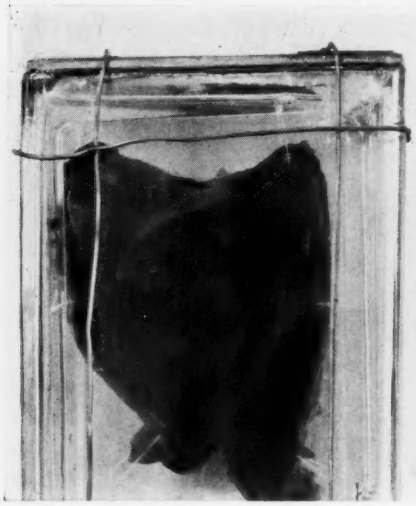

FIG. 17.—The advent of a purulent infection with rapid inflammation, distention, gangrene and necrosis.

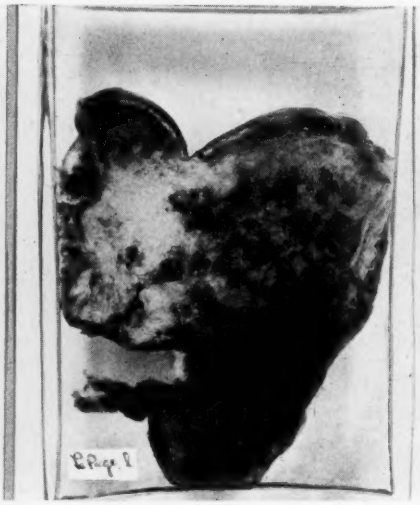

FIG. 18.—In the absence of a purulent infection, fibrosis of the gallbladder begins with chronic infection, the result of colon bacillus invasion.

in patients with active pain and colic that can be definitely ascribed to this organ.

The surgical importance of such a gallbladder, both with and without stones, has been very well established by the relief of colic afforded by its removal. In the absence of stones this type of gallbladder enlargement can

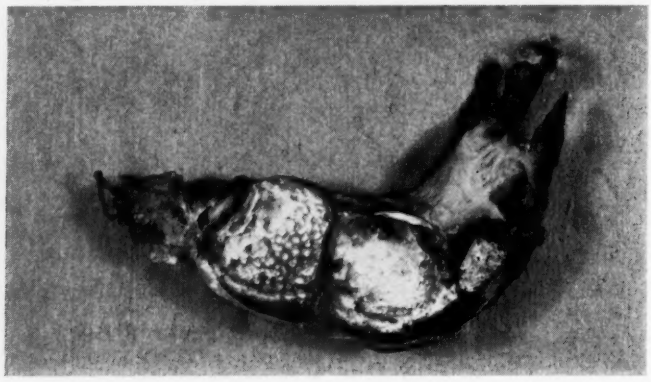

FIG. 19.—Further retraction with fibrosis and the formation of the "Black Jack" gallbladder containing little or no detritus and contracted tightly down upon the stones.

be successfully treated medically by the ordinary Sippy routine of alkalinization with frequent feedings to enhance its emptying. Yet, as is frequently found in the treatment of duodenal ulcer, in this type of individual recurrences from interruption of routine make operation the simplest procedure.

However, after cholecystectomy, when the sphincter of Oddi has not been relaxed, or after tone has returned, these patients may again have colicky attacks, with dark bile obtained by the duodenal tube, crystalline sediment and every indication of an active phase of concentration and stasis in the common duct during a period of personal trouble, or other cause for hyperacidity and neuromuscular dysfunction of the stomach and duodenum. During such periods, the Sippy routine and sedatives will again be required for the relief of symptoms. Without such treatment, these patients may develop stones in the common duct during these active phases which may correspond to the activity which results in stone formation in the gallbladder before it is removed.

After the occurrence of stone, the additional pain from impaction and danger from ulceration and infection of the gallbladder make their removal one of the most clearly defined surgical indications.

From a purely surgical standpoint, the evolution and final stage of this type of gallbladder is shown in Figs. 12, 13, 14, 15, 16, 17, 18, and 19.

A further complication may occur in the evolution of this type of gallbladder when a stone of comparatively large size becomes impacted in the ampulla, causing dilatation of the cystic duct in which there are ahead of it and nearer the common duct two or three small stones that may be floated into the common duct. When removed, they present the same characteristics as those stones in the gallbladder. Four such instances have been encountered in the past one hundred patients operated upon. Therefore it is important to explore the common duct when stones are found impacted in the cystic duct.

NOTE.—The author wishes to express his appreciation to Dr. Charles G. Heyd and Dr. Edward W. Peterson for their assistance in selecting the specimens used to illustrate these observations.

THE RELATION OF CHOLECYSTITIS TO PATHOLOGIC CHANGES IN THE LIVER *

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CONTROVERSY still exists as to the relation of inflammation of the gallbladder to concomitant pathologic changes in the liver. While some believe that cholecystitis is the result of a primary hepatitis, others advance the view that the hepatic changes are secondary to the disease of the gallbladder. A third group of observers holds that inflammation of the gallbladder and pathologic changes in the liver are independent of each other. A review of the various contributions shows much which is contradictory and raises many questions for further elucidation.

Riedel,[1] in 1888, first called attention to the fact that there appeared to be an enlargement of the right lobe of the liver in cholelithiasis. This observation was subsequently confirmed by others. However, the investigation of the presence of liver pathology in acute and chronic cholecystitis received little attention until 1918. Graham,[2] at that time, published his observations and microscopic findings in sections removed from the liver edge near the gallbladder in thirty consecutive cases of biliary tract disease. The microscopic sections disclosed the presence of hepatitis, consisting of infiltrations of polymorphonuclear leukocytes and lymphocytes in the interlobular spaces and often a mild fatty metamorphosis of the cells. The intensity of the hepatic changes seemed proportionate to the severity of the cholecystitis. The liver in cases of chronic cholecystitis often revealed lesions typical of early biliary cirrhosis. In 1921, Peterman, Priest, and Graham[3] confirmed the latter's previous observations and conclusions.

Graham's statement that cholecystitis is constantly accompanied by hepatitis, and that infection of the gallbladder results from a primary hepatitis, has been widely accepted. Tietze and Winkler,[4] Genkin,[5] Genkin and Dmitruk,[6] Murayama,[7] Pettinari,[8] Vilardell and Llort,[9] MacCarty and Jackson,[10] Hadley,[11] Heilmann[12] and many others, have reported the constant presence of liver changes in diseases of the biliary tract. Judd, Nickel and Wellbrock[13] stated that hepatitis and cholangitis occurred routinely in the presence of cholecystitis.

While many others agreed that the gallbladder lesions were accompanied by hepatitis, several have questioned which organ was primarily involved. Koster, Goldzieher and Collens,[14] in a similar study, confirmed the presence

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of a hepatitis, but felt that the inflammation of the gallbladder was primary. Else, Rosenblatt and Davis[15] believed that the liver was involved by direct extension from an infected gallbladder. Heyd, MacNeal and Killian[16] concluded that hepatitis was almost always associated with gallbladder disease but that it might be primary or secondary.

In spite of the evidence apparently supporting the dictum that hepatitis invariably accompanies cholecystitis, other investigators not only expressed doubt as to whether the cholecystitis or the hepatitis was the primary lesion, but whether an actual relationship existed between the lesions of the gallbladder and those observed in the liver. Martin[17] called attention to several pertinent facts, well known but apparently neglected in previous discussions of this problem. He pointed out that one of the main functions of the liver was the destruction and disposal of bacteria and toxic substances brought to it throughout the life of the individual. Some of these were destroyed without evident reaction, but that all forms of an appreciable reaction, from a mild to a severe hepatitis, might occur. He felt that the hepatitis found with acute and chronic cholecystitis presumably had little or no clinical significance and did not appear to be an important element in causing clinical forms of cirrhosis.

Graham, in his studies, considered the presence of infiltrations of the portal fields with polymorphonuclear leukocytes and lymphocytes sufficient to make a diagnosis of hepatitis. Since this lesion is seen in a great variety of conditions, as Noble[18] and others have certainly demonstrated, it is questionable whether this may be called a hepatitis. Some, notably Tietze and Winkler, in addition to these periportal infiltrations, have reported changes in the liver cells, and Albot,[19] and Albot and Caroli[20] seemingly confirmed their findings by studies of the finer histology of the liver.

A further effort has again been made in this communication to study the question of the relationship of disease of the biliary tract to pathologic changes in the liver, with special emphasis upon the finer cytology of the liver.

Materials and Methods.—A special attempt was made to secure liver sections deep within the organ to obviate the current criticism that sections from the surface cannot be taken as an index of changes occurring throughout the liver. The gross pathology of the liver, gallbladder and bile ducts was carefully noted at operation. The gallbladder was aspirated of its fluid contents and a retrograde cholecystectomy performed when indicated. The excised gallbladder was then completely emptied, the cystic duct ligated and the organ was immediately distended with an amount of formalin equal in quantity to the aspirated bile. The distended gallbladder was immediately fixed in formalin. It was subsequently cut longitudinally so that a better idea might be gained as to the pathologic changes involving the entire organ. Sections were stained with hematoxylin and eosin, Weigert's elastica, and the iron-hematoxylin-van Gieson. Bacterial stains were performed on many of these sections.

Specimens of liver were taken either from the dome of the right or left

lobe, 2.5 to 3 cm. deep to the surface. The Hoffman biopsy punch was used routinely and was found excellent for this purpose, permitting the removal of pieces of liver tissue sufficient for study. Over 100 biopsies were performed and no untoward results could be traced to this procedure. If the liver bled profusely through the puncture, a plain or iodoform pack placed against the bleeding area and left in place for twenty-four hours controlled the hemorrhage and prevented any further complications.

The liver tissue was divided into three portions and fixed immediately in 10 per cent neutral formalin, absolute alcohol, and Regaud's solution. Hematoxylin and eosin, fat, glycogen, and Altmann's mitochondrial stains were performed routinely.

Histologic Findings.—The histology of the gallbladder was studied mainly in order to classify the degree of the inflammatory process present. This was done to determine whether any relationship existed between the acuteness of the cholecystitis and the changes observed in the sections of liver removed by biopsy.

The pathologic findings in the gallbladders were classified into two groups. Those in which a predominantly acute inflammatory process was present were placed in Group I, although many exhibited signs of a previous chronic inflammation, and stones. The second group, all of which were cases of cholelithiasis, consisted of those in which chronic inflammation dominated.

The histologic findings of the liver sections fell into two groups determined by the absence or presence of jaundice at the time of operation. These two groups were correlated with the previous classification of the gallbladder as follows:

GROUP I.—JAUNDICE ABSENT AT THE TIME OF OPERATION* (TABLE I)

(a) Acute cholecystitis..... 11 cases
(b) Chronic cholecystitis..... 29 cases

* Cholecystectomy performed in thirty-seven cases, and cholecystostomy in three.

TABLE I

A.—*Eleven Cases of Acute Cholecystitis without Jaundice Subjected to Biopsy of the Liver*

Case No.	Operation	Previous History of Jaundice	Preoperative Icteric Index	Bilirubin Mgms. per 100 cc.
1	Cholecystectomy	None	7	0.2
2	Cholecystectomy	None	12	0.7
7	Cholecystectomy	None	14	0.6
34	Cholecystectomy	Slight	10	0.4
72	Cholecystectomy	None	—	—
74	Cholecystectomy	None	8	0.2
81	Cholecystectomy	None	17	0.2
82	Cholecystectomy	None	8	0.2
84	Cholecystectomy	None	6	—
18	Cholecystostomy	None	10	0.3
46	Cholecystostomy	None	6	0.2

TABLE I (*Continued*)

B.—*Twenty-nine Cases of Chronic Cholecystitis without Jaundice Subjected to Biopsy of the Liver*

Case No.	Operation	Previous History of Jaundice	Preoperative Icteric Index	Bilirubin Mgms. per 100 cc.
3	Cholecystectomy	None	—	0.2
5	Cholecystectomy	None	12	0.3
8	Cholecystectomy	None	12	0.3
10	Cholecystectomy	None	14	0.2
11	Cholecystectomy	None	12	0.2
13	Cholecystectomy	None	5	0.2
14	Cholecystectomy	None	13	0.3
16	Cholecystectomy	None	6	0.6
20	Cholecystectomy	None	15	1.5
22	Cholecystectomy	None	18	0.6
25	Cholecystectomy	None	26	0.2
33	Cholecystectomy	None	8	0.2
39	Cholecystectomy	None	14	1.0
40	Cholecystectomy	None	7	0.2
41	Cholecystectomy	None	28	3.5
44	Cholecystectomy	None	5	0.2
47	Cholecystectomy	None	17	1.1
48	Cholecystectomy	Repeated attacks	10	0.2
50	Cholecystectomy	None	8	0.2
54	Cholecystectomy	None	13	0.6
58	Cholecystectomy	Single attack	6	0.2
60	Cholecystectomy	None	12	0.3
63	Cholecystectomy	None	8	0.2
64	Cholecystectomy	None	10	—
70	Cholecystectomy	Single attack	9	0.2
73	Cholecystectomy	None	8	0.2
79	Cholecystectomy	None	7	0.3
83	Cholecystectomy	None	10	0.5
23	Cholecystostomy	Repeated attacks	15	0.5

GROUP II.—JAUNDICE PRESENT AT THE TIME OF OPERATION* (TABLE II)

(a) Acute cholecystitis..... 6 cases
(b) Chronic cholecystitis..... 3 cases

* Cholecystectomy performed in seven cases, and cholecystostomy in two.

TABLE II

A.—*Six Cases of Acute Cholecystitis with Jaundice Subjected to Biopsy of the Liver*

Case No.	Operation	Previous History of Jaundice	Preoperative Icteric Index	Bilirubin Mgms. per 100 cc.
24	Cholecystectomy	None	45	2.5
35	Cholecystectomy	None	45	3.0
42	Cholecystectomy	Transient	—	—
59	Cholecystectomy	None	40	0.5
28	Cholecystostomy	None	65	3.5
51	Cholecystostomy	Repeated attacks	48	3.5

TABLE II (*Continued*)

B.—*Three Cases of Chronic Cholecystitis with Jaundice Subjected to Biopsy of the Liver*

Case No.	Operation	Previous History of Jaundice	Preoperative Icteric Index	Bilirubin Mgms. per 100 cc
21	Cholecystectomy	Single attack	18	0.8
37	Cholecystectomy	None	25	1.2
49	Cholecystectomy	None	30	—

There were, in addition, two cases in which the gallbladder had been removed previously and secondary operation disclosed a complete stricture of the common bile duct in one, and incomplete obstruction by choledochal stone without jaundice in the other.

A group of cases were chosen to serve as controls. These comprised one of acute cholangitis with jaundice, seven presenting common duct obstruction with icterus due either to malignancy of the biliary tract, or of the head of the pancreas, and three in which there was no demonstrable disease of the gallbladder or liver.

In order to appreciate the findings present in the liver sections obtained by biopsy, it is necessary to point out certain histologic features of the normal liver. As a rule, a moderate number of lymphocytes and occasional polymorphonuclear leukocytes are found in the periportal connective tissue of the adult liver, more frequent in the smaller portal fields.[21, 22] The presence of an increased number of round cells, together with an increase in the polymorphonuclear leukocytes and the presence of eosinophiles, can be considered pathologic.

The normal liver cells contain varying quantities of fat, dependent upon the state of nutrition of the liver cell. Brown pigment granules are often seen, and when present are found in the vicinity of the central vein.

In the normal liver lobule, small groups of cells with dark cytoplasm and small, deeply stained nuclei are often seen about the portal fields, less commonly about the central vein, and more rarely in small numbers in the middle zone of the lobule. These "dark" cells contrast sharply with the remaining liver cells, which are larger, possess a lighter staining cytoplasm, and a bigger, lighter staining nucleus with large nucleoli. The latter are termed "clear" or "light" cells. The significance of the "dark" cells has not been fully explained. Most investigators believe that they represent cells, either in a resting phase, or in a state of functional exhaustion.[23, 24] The "clear" cells are considered to be physiologically active. The "dark" cells are devoid of glycogen, whereas the "clear" cells usually contain much glycogen and small fat droplets as well. Striking differences between the "dark" and "clear" cells are further evidenced by mitochondrial studies. In the "dark" cells, the mitochondria are closely packed or massed in the central portion of the cell, close about the nucleus, and do not appear along the cell membrane. Mitochondria are seen to be more or less evenly dispersed throughout the

"clear" cell, with distinct cytoplasmic spaces between groups or individual mitochondria. The distribution of the mitochondria in the "clear" cells depends to a great extent upon the amount of glycogen and fat present. If the cell contains much glycogen and fat, the mitochondria are pushed far apart and are unevenly dispersed throughout the cell. This dispersion imparts a very clear appearance to the cells, a condition which has been termed "clarification." These facts become more evident when a comparison is made between the glycogen, hematoxylin and eosin, and mitochondrial stains.

Some observers, particularly Albot in an interpretation of liver damage produced experimentally, have considered that both "clarification" and the presence of "dark" cells represent pathologic states. This has not been substantiated in these histologic studies.

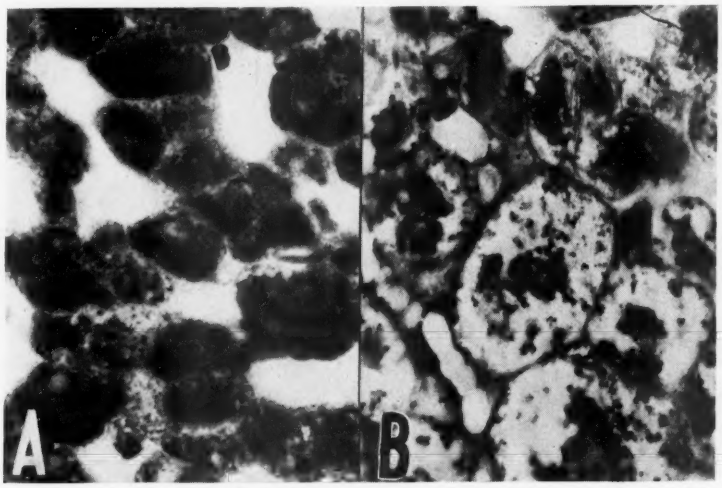

FIG. 1.—Liver of carrot-fed rabbit. (A) Best's carmine stain. All the cells are filled with glycogen. (B) Altmann's mitochondrial stain. Note the large, "clear" cells with dispersion of the mitochondria.

A series of experiments on rabbits was undertaken to study this particular problem. One group of rabbits was fed a diet of carrots for three days, another was starved for a similar period, and a third was kept on an average diet. The animals were then sacrificed, and sections of the liver were fixed at once and stained for glycogen, fat and mitochondria. It is well known that rabbits fed with carrots store an enormous amount of glycogen in the liver, whereas starvation will rapidly deplete the liver of glycogen. A study of the liver cells in the carrot-fed rabbits demonstrated that the presence of glycogen produces a marked enlargement of the cell, decided "clarification" and a dispersion of the mitochondria (Fig. 1). The liver cells of the starved rabbits were small, dark, devoid of glycogen and uniformly presented a massing of the mitochondria in the center of the cell (Fig. 2). Similar changes were noted by Hall and Mackay[25] in a study of the relation of mitochondria to glycogen in the rabbit liver cell. The conclusion may be drawn that the phenomenon of "clarification" or the presence of "dark" cells merely represents anatomic states dependent upon the physiologic activity of the cell.

The appearance of the mitochondria is of significance as an index of the physiologic or pathologic state of the liver cell, and is of great importance in the study of early parenchymal changes. Numerous investigators have established the fact that the earliest evidence of cell degeneration is to be found in alterations of the mitochondria.[26] These have been observed to change twenty-four hours before the nucleus disintegrates.[27] Pathologic alterations of the mitochondria are evidenced by a change in shape, with subsequent diminution in number, and disappearance by dissolution.[27, 28] The shape of the mitochondria, which is normally either filamentous, or in the form of short, thick rods, or small granules, changes to a large globular form under abnormal conditions.[27] These globules are now seen as discrete bodies within the cell, in no particular relation to the nucleus. As the degeneration pro-

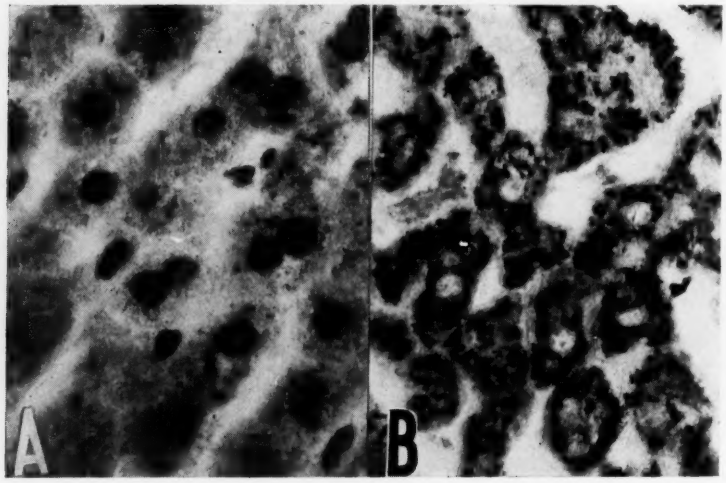

FIG. 2.—Liver of starved rabbit. (A) Best's carmine stain. All the cells are devoid of glycogen. (B) Altmann's mitochondrial stain. Note the small, "dark" cells with compact massing of the mitochondria.

ceeds, the number of mitochondria in the cell is appreciably diminished, and ultimately the mitochondria completely disappear. Occasionally, mitochondria, although visible, lose their staining properties in the process of impending dissolution. It must be constantly borne in mind, however, that the mitochondria are affected by the various technical procedures involved in the preparation of sections.[28] Great care must, therefore, be exercised in ascribing pathologic significance to changes in shape and form.[28]

The microscopic appearance of the liver with reference to its finer histology, especially the mitochondria, will now be detailed in the cases in this series.

GROUP I.—*No jaundice present at the time of operation.*—(*a*) Acute cholecystitis. There were eleven cases in this group. An infiltration of the periportal connective tissue with round cells was seen in nine, and in two of these the presence of an increased number of polymorphonuclear leukocytes was noted. No infiltration was observed in two cases. The inflammatory cells

were present in the connective tissue about the small vessels, bile ducts, and in the lymphatic spaces, but never within the wall or lumen of a bile duct. Polymorphonuclear leukocytes were only occasionally seen in increased numbers in the sinusoids. When present, they were usually observed in the capillaries about the portal fields. Fat was present in moderate amounts in seven instances, generally localized to the cells in the middle or central portions of the lobule. In many cases, the cells adjoining the central veins contained brown pigment. Glycogen was usually present in abundance. Areas of "clear" cells of varying extent, chiefly confined to the central and middle portions of the lobule, were seen to alternate with areas of "dark" cells. This was characteristic of all sections. The distribution of the mitochondria of the "clear" and "dark" areas was readily correlated with the presence or absence of glycogen. As in normal liver sections, glycogen-containing cells were large, clear, and showed the characteristic dispersion of the mitochondria, in contrast to the close packing of the mitochondria in the small, dark cells (Fig. 4 A). There were no pathologic alterations of the mitochondria.

(*b*) Chronic cholecystitis. There were twenty-nine cases in this group. A slight to marked infiltration of the periportal connective tissue by lymphocytes, plasma cells, and in some instances, polymorphonuclear leukocytes was noted in twenty. The lymphocytes and polymorphonuclear leukocytes were also seen in small quantities in the capillaries about the portal field in six instances. The distribution of the inflammatory cells within the periportal connective tissue was identical with that described in the cases of acute cholecystitis, essentially an infiltration about the small vessels, bile ducts and in the lymphatic spaces (Fig. 3 A). Infiltrations of the walls or lumina of the bile ducts were not noted. The periportal connective tissue was increased, with a widening of the portal field in several instances. Occasional bands of connective tissue were seen to extend for a short distance into the liver lobule from the widened portal field, sometimes surrounding small islands of unaltered cells (Fig. 3 A). Observations on the fat, pigment, glycogen and mitochondria of the cells (Fig. 4 B) were similar to those described in the cases of acute cholecystitis.

GROUP II.—*Jaundice present at the time of operation.*—These cases will be discussed together since they presented features which were identical in all respects. This group comprised six cases of acute cholecystitis, three of chronic cholecystitis, and one of common duct obstruction by choledochal stone occurring several months after cholecystectomy. Cholecystectomy was performed in seven cases and cholecystostomy in two.

A study of the liver sections unquestionably revealed a more marked infiltration of the periportal connective tissue by lymphocytes, plasma cells, occasional histiocytes, with polymorphonuclear leukocytes in abundance. Those cells often extended into the adjoining sinusoids. Occasional infiltration of the walls and lumina of the small bile ducts was observed in one instance (Fig. 3 B). The bile capillaries were dilated and filled by bile thrombi in

more than one-half of the cases. The extent of the bile capillary occlusion varied markedly. The liver cells in the immediate vicinity of these occluded bile capillaries often contained bile pigment granules and occasionally ex-

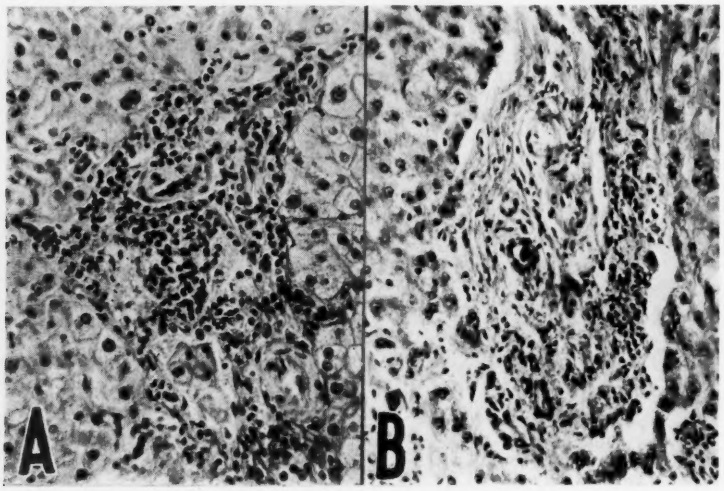

FIG. 3(A).—(Case LXX.) Chronic cholecystitis without jaundice. Infiltration of the periportal connective tissue with round cells and few polymorphonuclear leukocytes. There is some proliferation of the periportal connective tissue, which extends out into the lobule and isolates a small group of liver cells. (Hematoxylin and eosin.) (B) (Case LI.) Chronic cholecystitis with jaundice. Infiltration of the periportal connective tissue by inflammatory cells. There is some widening of the portal field. A small bile duct in the center contains several polymorphonuclear leukocytes. (Hematoxylin and eosin.)

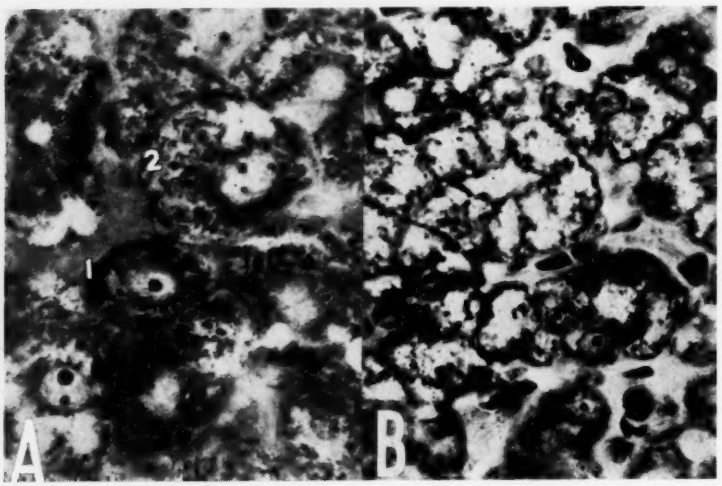

FIG. 4(A).—(Case XXXIV.) Acute cholecystitis without jaundice. Altman.'s mitochondrial stain. Typical field showing "dark" (1) and "clear" (2) cells, with normal mitochondria. (B) (Case XXXIII.) Chronic cholecystitis without jaundice. Altmann's mitochondrial stain. Large area of "clear" cells with normal mitochondria.

hibited nuclear and cytoplasmic degeneration. These changes were more striking in areas exhibiting extensive and large bile capillary thrombi. Cell degeneration was not noted when capillary thrombi were not present. The

glycogen, fat and pigment content of the cells differed in no way from that observed in the nonjaundiced cases. While many cells containing bile pigment did not show the presence of glycogen, bile pigment and glycogen were often observed together in other cells.

The cases in which bile thrombi were minimal in extent or absent (about one-half of the group) presented no unusual changes in the mitochondria. Their appearance was identical with that seen in the nonjaundiced cases. However, striking alterations were present in the mitochondria of the cells in the immediate vicinity of extensive capillary bile thrombosis. These were manifested by the characteristic changes seen in mitochondriolysis (Fig. 5).

The mitochondrial stains served as a more reliable index of cell degeneration than hemotoxylin and eosin. The mitochondria of cells distant to the areas of bile thrombosis were unaltered.

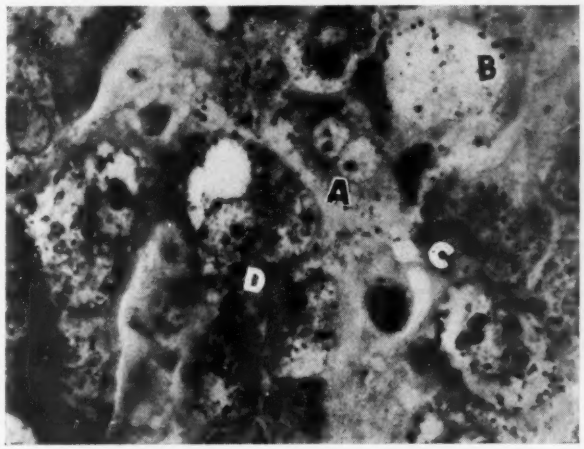

FIG. 5.—(Case XXVIII.) Acute cholecystitis with jaundice. Altmann's mitochondrial stain. Cells adjoining bile capillary thrombi (C) showing absence of mitochondria (A) and globular forms with diminution in number (B). Remaining cells (D) show normal mitochondria.

A comparison of the sections obtained from the livers in cases of cholecystitis with choledochal stones, and those obtained from cases of common duct obstruction due to malignancy of the biliary tract or the head of the pancreas, in which long-standing jaundice was present, showed either identical or more pronounced mitochondriolysis. In the latter these alterations were seen likewise only in the areas of bile capillary thrombi.

The liver sections in one case of acute cholangitis showed infiltration of the walls and lumina of the bile ducts with polymorphonuclear leukocytes, desquamation of the epithelium of the bile ducts, in addition to infiltration of the portal fields. Foci of capillary bile thrombi were present throughout and cells in their vicinity showed the same striking mitochondriolysis.

Summary of the Histologic Findings.—Studies of sections of liver removed by biopsy in forty cases of acute and chronic cholecystitis, in which jaundice was not present at the time of operation generally presented infiltration of the portal fields by lymphocytes, occasional plasma cells, and polymorphonuclear leukocytes. This infiltration was limited to the periportal tissues and did not selectively involve either the perivascular or periductal regions, or the walls, or lumina of the bile ducts. A proliferation of the periportal connective tissue was occasionally noted. The fat, glycogen, and pigment

content of the liver cells was within normal limits. The mitochondria showed no deviations from the normal.

The liver sections from patients with jaundice presented the same periportal infiltrations, but usually more marked in extent. Proliferation of the periportal connective tissue was seen more frequently. The bile capillaries were dilated, and filled by bile thrombi in about one-half of the cases. Occasional liver cell degeneration, as evidenced by definite mitochondrial alterations, were observed about these capillary bile thrombi. The extent of mitochondriolysis was proportional to the severity of the bile capillary obstruction. Mitochondrial changes were not seen in the absence of bile capillary thrombi despite the clinical evidence of jaundice. The liver cells contained fat, glycogen and pigment, within normal limits.

Discussion.—Sections removed from the edge or surface of the liver are prone to present pathologic alterations which cannot be considered as representative of the organ as a whole. Metzler,[29] Enders,[30] and others have shown that with advancing age there is an atrophy of the liver edge, with an increase in the connective tissue of the portal fields in this area. Long-continued, mild external trauma, such as pressure from the rib margins and chronic inflammation in the upper quadrant of the abdomen with the formation of localized peritoneal adhesions, may be additional factors accounting for the scarring of the liver edge and surface. Certainly the liver tissues immediately adjacent to an infected gallbladder may show localized inflammatory reactions. It is, therefore, essential in order to properly evaluate the hepatic changes in diseases of the biliary tract to obtain sections from the deeper portions of the liver parenchyma at some distance from the gallbladder fossa. Sections in this study were taken deep to the dome of either the right or left hepatic lobes.

The majority of these investigations in the past has been limited to routine histologic studies. This method is frequently inadequate. A mere granular appearance of the cytoplasm cannot be taken as evidence of cell degeneration, unless this is confirmed by mitochondrial studies. Likewise, many have interpreted the presence of fat in the cells as evidence of fatty degeneration. Fat in the liver cell is a physiologic condition unless present in unusually large amounts. Misinterpretation may result in ascribing pathologic significance to varying physiologic appearances of the liver cell. The presence of small "dark" cells, or very large "clear" cells has been considered to represent a pathologic state. These appearances are physiologic, as this study and other investigations have shown.

A study of the liver parenchyma, with special emphasis on the finer cytology, showed no pathologic changes in all cases of cholecystitis without jaundice in this series. The hepatic changes in this type of case reported by many,[4, 20] were not confirmed. However, in a series of cases with jaundice due to common duct obstruction by stone, in one case of acute cholangitis and in seven cases of obstructive jaundice, resulting from malignant tumors of the biliary tract or the head of the pancreas, the process of cell destruction could be verified by the alterations of the mitochondria. Mitochondriolysis, and to a lesser de-

gree concomitant nuclear and cytoplasmic changes, were observed only in the vicinity of bile capillary thrombi. This destruction was due to changes incident to obstruction. It bore no relationship to the changes occurring in the gallbladder. The extensive necrosis of liver cells reported by some observers[4] was not confirmed in this study.

Nearly all the investigators have stressed the presence of periportal cellular infiltration in biliary tract disease. This infiltration of inflammatory cells was present in varying degrees in all the cases considered in this study, more marked, however, in those instances in which jaundice was present at the time of operation. Periportal connective tissue proliferation was observed in a number of instances of chronic cholecystitis. These patients, not infrequently, gave a history of previous attacks of icterus.

Periportal cellular infiltrations have been interpreted as evidence of cholangitis and pericholangitis. A diagnosis of cholangitis cannot be made unless there is a cellular infiltration of the walls or lumina of the bile ducts, with consequent widening, desquamation of the epithelium and the presence of an intraductal exudate. However, many have ventured a diagnosis of cholangitis, in spite of the fact that these criteria were not satisfied by their protocols. It is incorrect to state that a pericholangitis exists unless the presence of a cholangitis is assured. A diagnosis of pericholangitis based only upon the presence of cells about a bile duct, as seen in the normal course of a periportal infiltration, is not justified. Furthermore, a periportal infiltration associated with periductal orientation of cells is observed in many other conditions in which the disease of the biliary tract can be excluded definitely by detailed postmortem studies.

Kahlstorf[22] examined the liver in 207 necropsies and found periportal infiltrations in disease of the biliary tract, chronic and acute disease of the gastro-intestinal tract, and in 92 per cent of general infections. He concluded that periportal infiltrations are inflammatory in nature, analogous to other inflammatory conditions inasmuch as polymorphonuclear leukocytes were noted in acute processes, and lymphocytes, plasma cells and histocytes in the chronic processes. Kettler,[21] in a similar study, concurred in this view and stressed especially the presence in general infections of these infiltrations which may remain long after the initial disease had subsided. While he believed these inflammatory reactions could lead to a slight scarring of Glisson's capsule, they never produced a cirrhosis, and were without clinical significance. Noble likewise studied the liver in 212 routine necropsies and found periportal infiltration in all but two instances. He gave no explanation for the constant presence of these cells, but believed that they were unrelated either to general infections or to any specific type of disease. Noble found that nonclinical cholecystitis was frequently accompanied by periportal infiltrations and agreed with Martin[17] that the inflammation, *i.e.*, the presence of periportal cells, could be secondary to the presence of bacteria and toxic substances carried to the liver by the portal blood.

Periportal infiltrations, obviously, are not a reaction of the liver specific for biliary tract disease.

The proliferation of the periportal connective tissue in instances of long-standing biliary tract disease can be explained both by periportal irritation and by bile stasis in cases with obstructive jaundice.

Jaundice, although latent, with an icteric index of 16 to 18, may not be evident clinically in incomplete obstruction of the common duct. If, then, this condition of latent jaundice exists over prolonged periods of time, focal liver cell degeneration will result in areas of bile capillary thrombosis and proliferation of the periportal connective tissue will ensue. This is essentially what happens in cases of chronic cholecystitis in which previous attacks of jaundice were present, or in which the icterus has been latent. This histologic picture has been interpreted as indicative of early biliary cirrhosis. Such an interpretation is not justified since the proliferation of the periportal connective tissue is only focal in character.

The use of the term "hepatitis," without qualification, is incorrect when applied to those cases of biliary tract disease without jaundice in which only periportal infiltrations without any liver cell changes are present. Even the additional presence of focal liver cell damage, in cases of cholecystitis with jaundice, is not indicative of hepatitis. Hepatitis is a primary disease of the liver characterized by an inflammatory process in the framework associated with diffuse parenchymal changes. This was not found in biliary tract disease.

The use of the term "interstitial hepatitis" may be justified from the mere morphologic point of view. However, inasmuch as periportal infiltrations are very frequently indicative of a reaction to extrahepatic infection and do not represent a primary inflammation of the liver, the diagnosis of "interstitial hepatitis" loses its significance in these instances.

The designation "focal hepatosis" may be used in obstructive jaundice with focal cell degeneration. It is unlikely that transient attacks of obstructive jaundice will lead to serious parenchymal alterations. Obstructive jaundice over prolonged periods, however, results in both advanced parenchymal and interstitial alterations, representing true biliary cirrhosis.

Conclusions

Biopsy of the liver was performed in 40 cases of acute and chronic cholecystitis without jaundice, and in nine with jaundice. Studies with finer histologic technic revealed no changes in the liver cells in biliary tract disease without jaundice. Focal liver cell degeneration seen in cases with jaundice represents a reaction to bile stasis and is in no way related to the primary disease of the gallbladder. The periportal infiltrations observed in biliary tract disease are not specific for the disease, but represent a reaction of the liver to extrahepatic infection. Hepatitis is not an accompaniment of cholecystitis as evidenced by the absence of inflammatory and parenchymal changes in the liver.

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DISCUSSION.—DR. WALTON MARTIN (New York) pointed out that Doctor Colp, by taking sections of the liver distant from the bed of the gallbladder, had demonstrated that the liver parenchyma shows no evidence of pathologic change, studied with special emphasis on the finer cytology, in cholecystitis without jaundice. He said further that at the time Doctor Graham presented his views regarding the interrelation of hepatitis and cholecystitis his arguments seemed unconvincing insofar as they did not take sufficiently into account the distinction between hepatitis contiguous to the inflamed gallbladder and which would be expected about any focus of infection and generalized hepatitis; secondly that he placed no stress on the well-recognized observation that disturbance of the liver cells inevitably follows the slightest infection or blocking of the excretory duct of the liver following a law that is common to all glandular structures—the kidney, the pancreas, the mammary and salivary glands, *et cetera,* and that he failed to recognize the frequency of the reaction of the liver cells to all manner of toxic agents brought to it by the blood stream.

Moreover, Graham's views do not seem to be in accord with common clinical experience such as the prompt return to vigorous health after the removal of a severely infected gallbladder even with a history extending over years, provided that there has been no involvement of the common duct, the follow up on these cases showing neither cirrhosis nor hepatitis. Further severe infections of the liver such as are seen with pyogenic infection of the portal vein are not accompanied by corresponding cholecystitis and autopsies on acute hepatitis do not show gross lesions of the gallbladder; neither do the specific infections such as tuberculosis or syphilis set up as a rule specific cholecystitis. Tuberculosis of the gallbladder is extremely rare, although small tuberculous lesions are nearly always present in the liver of tuberculous patients if careful search is made according to Calmette.

DR. CHARLES GORDON HEYD (New York) said that any discussion of changes in the liver, incident or sequential to abdominal infection, should be prefaced by a consideration of Adami's paper on "Subinfection" and the studies of Mallory on "Toxic Lesions of the Hepatic Cells." It is widely held, Doctor Heyd thought, that the liver and spleen, separately or jointly, act as sieves to strain out bacteria. The performance of an Eck's fistula demonstrates that all of the subjects died in six to eight weeks of a general septicemia. Without the interposition of the liver between the portal system and the general circulation, few people could survive as septicemia would be the rule. When considering changes in the liver, it is important to remember that one of the vital functions of the liver is regeneration. An individual maintains relatively good liver functional capacity if and when the regenera-

tive process is equal to any simultaneous degenerative process. Furthermore, in the microscopic lesions in the liver one must approach the study from two points of view: Is the primary liver injury in the course of the biliray system, or is the primary liver damage through the central vein of the portal vascular system?

Doctor Heyd felt that it was unfortunate that Doctor Colp had introduced the changes in the liver cells in patients with obstructive jaundice as pertinent to his study. The pathologic changes in the liver in the presence of obstructive jaundice are obviously gross, for within a very short time after the initiation of an obstructive jaundice there is a progressive degeneration of liver cells and the liver, either locally or somewhat generally, is the site of an intense chemical and possibly infective irritation and the result is a tremendous edema of the liver. At operation, one is profoundly impressed by the gross appearance of the liver in the presence of a long-continued jaundice, as brought before the New York Surgical Society by Doctor Heyd in April, 1926, and again in January, 1928.

The greatest degree of liver enlargement in obstructive jaundice is due to the serum edema and if these livers are removed at autopsy and suspended in toto as much as 500 to 100 cc. of serum can be obtained by drainage.

There are certain types of liver injury that do occur in infection of the gallbladder and bile ducts without jaundice. In one of Doctor Heyd's cases, from a portion of liver removed at operation it was possible to trace sequential pathologic stages from the gallbladder up to polynuclear cells on or about the smallest collecting bile canaliculi. When one discusses the changes that occur either primarily in the liver by means of the portal system or secondarily from gallbladder infection, Doctor Heyd believed some of the pathologic inferences of Doctor Colp and his associates are, in a measure, justified. To be sure, the authors were handicapped by the small size of their biopsy specimens, and their studies of the liver cell for mitochondriacal bodies are certainly of value in indicating degenerative changes in the individual cells within the hepatic columns. It is not proper, however, to regard such changes in the individual cells as evidence of inflammation. The work presented by Doctor Colp deals very definitely with changes in the liver cells due to obstruction and intoxication, but has relatively little relationship to actual hepatitis in which the framework of the liver shows markedly definite changes.

Dr. Allen O. Whipple (New York) mentioned the fact that an adequate study of portal blood bacteriology, both aerobic and anaerobic, has not as yet been made in human cases. Such a study, he said, would give valuable evidence in regard to the problem of periportal infiltration and the ability of the liver to take care of bacterial invasion. It was stressed by Doctor Colp and emphasized by Doctor Martin that the tissues examined in Doctor Colp's series were not in the immediate neighborhood of the gallbladder. In the past, certainly, tissues removed for examination have been those most easily removed from the edge of the right lobe of the liver in the neighborhood of the gallbladder. These should not be taken as criteria of the liver pathology as a whole.

THE SEQUELAE AFTER CHOLECYSTOSTOMY

WITH SPECIAL REFERENCE TO CHOLELITHIASIS

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THIS paper represents a study of 500 cases of gallbladder disease from 1921 to 1932. In this series there were 125 cholecystostomies, 151 cholecystectomies, and 224 cases upon whom no operation had been performed. The mortality of the first group was 16 per cent, of the second 2 per cent, and of the third 1.3 per cent. No attempt is being made to present a complete résumé of the drainage cases but rather to indicate features that have been of special concern to our observers in the Follow-up Clinic of the Third Surgical Division of the Bellevue Hospital.

Of these 125 cholecystostomies follow-up data were obtained in 87. Five individuals subsequently underwent cholecystectomy for stones after an average duration of ten years. Four submitted to removal of the gallbladder for biliary fistula after a mean period of two years. Twenty-two of these return patients complained of pain in the operative scars or within the abdomen and not directly attributable to the gallbladder. In this latter category belonged two with syphilis, three with carcinoma, two upon whom gastroenterostomy had been performed, and seven with herniae. Thirty-nine patients have apparently remained entirely symptom-free or 46 per cent of the 87 who returned after drainage of the gallbladder.

It is noteworthy that but two of these individuals gave evidence of diabetes and continued under treatment at the Diabetic Clinic, although it is known that the typical patient with calculus cholecystitis presents a hyperglycemia with or without glycosuria before operation. Harrison has constructed a summation curve for the "gallbladder" and one for the "non-gallbladder" patient and finds that this diminished sugar tolerance in the gallbladder case corresponds remarkably with that of the blood sugar of the experimental series previously reported.[1, 2, 3] Furthermore, it is gratifying that definite progress in the apparent arrest of pancreatitis followed drainage of the bladder especially in a group of cases recognized to be the most acutely ill of all the gallbladder series. Conversely, it is interesting to compare Joslin's[4] observation that 15 per cent of 400 of his diabetics two years previously had been diagnosed as cholelithiasis. He advised cleaning up the bladder infection; and cholecystostomy appears to have aborted "pre-diabetics" in this series.

The incidence of approximately eight per cent seems high for postoperative herniae. Many factors appear to enter into this incisional rupture. The patients were obese manual workers of the clinic type. They were

difficult to protect against wound strain because even among those for whom proper abdominal supports had been obtained there were those who admitted wearing the corsets only when they dressed up to go out while they saved them and put on any old and probably worthless supports to do the scrubbing and washing. Nor would they properly attend to their diets. They continued to increase in weight after operation notwithstanding most of these people were already too obese when first observed. The use of two drains at the upper angle of the cholecystostomy wound is not believed *per se* to substantially increase herniation over that of the cholecystectomy wound with one drain. But the drainage is greater and more prolonged in the cholecystostomy patient, and the discharge may and often does contain digestive ferments through reflux of duodenal secretion through an incompetent bilioduodenal sphincter and the common bile duct. This discharge too often finds it way through the fat layer of the wound to the lower angle most often during the second postoperative week. When the patient is elevated on a backrest this makes counterdrainage necessary, and delays the healing of the wound. Therefore prolonged irritating discharges from the bladder should probably be considered an important causative factor along with overweight, faulty diet, overstrain, and the mechanical presence of the two drains in the production of incisional hernia following cholecystostomy.

Herniation of the wound is a complication of the operation, but fistula and stone recurrence indicate unresolved cholecystitis with or without cholangitis. This latter condition, amounting to 21 per cent of the return drainage cases, detracts from the operation of cholecystostomy as a permanent means of treating cholelithiasis.

Biliary fistula occurred in 11 per cent of the postoperatives of this series. This complication is not to be regarded as unfavorable in that these particular individuals occasionally developed chills and fever if the fistulae were tem-

TABLE I

Showing Effect upon Human Gallstone Left in Normal Canine Gallbladder

Exp. No.	Duration in days	Color	Wt. gr. before	Shape	Color	Wt. gr. after	Shape	Net loss gr.
25	20	White	2.0	Facetted	Brown	1	Ovoid	1.0
26	26	White	31.0	Mulberry	0	0	0	31.0
36	25	Yellow	15.5	Mulberry	0	0	0	15.5
45	126	White	9.28	5 facets	0	0	0	9.28
50	60	Brown	18.5	Ellips'l	Brown	8.5	Ellips'l	10.0
57	77	Green	2.75	3 facets	0	0	0	2.75
		Green	6.5	4 facets	0	0	0	6.5
81	84	Brown	18.5	Mushroom	Brown	16	Mushroom	2.5
90	63	Green	7.38	7 facets	0	0	0	7.38

Roentgenograms of all bladders after tetrachlorphenphthalein excepting Nos. 45 and 50 were negative for stones.

porarily closed. Chronically diseased functionless bladders kept up inflammation and required drainage of the exudate or allowed stones to reform. In two of these patients with fistulae epitheliomata developed about the external openings. Reoperation and cholecystectomy were successful in the four cases of this group who consented to rehospitalization.

The chief interest in this report has been the recurrence of stones. Five of the cases reoperated upon were found to have stones; but there were three additional with positive cholecystograms, and one clinically diagnosed cholelithiasis. These nine indicate an approximate ten per cent recurrence after cholecystostomy.

The etiology of stone formation in gallbladders has been under investigation. It was long thought to be associated in some way with biliary stasis. Recently conditions under which concretions take place have been more definitely stated.

It is generally understood that gallstones are the product of abnormal conditions within the biliary tract and that stones disappear if exposed to normal bile within a normal bladder. Phemister, Day, and Hastings[5] in a series of animal experiments supplementing observations upon 48 human cases of cholelithiasis concluded that "obstruction to the outlet of the gallbladder at least of a high degree and a low grade chronic inflammation are essential for the formation of separate deposits of calcium carbonate in the gallbladder." They further state that calcium is derived from the wall of the bladder and when thrown down in sufficient amount precipitates. Andrews,

TABLE II

Showing Effect upon Human Gallstone of Ligation of Cystic Duct

Exp. No.	Duration in days	Condition of bladder (after)	Glands	Pancreas	Stone wt., gr. before	Stone wt., gr. after
90B	3	Thickened			5.75	6.50
91	5	Ac. inflam.			7.0	7.125
94	17	Thickened	Enlarged		1.0	0
101	31	Ac. inflam.		Thick	6.0	7.25
102	31	Ac. inflam.	Enlarged	Thick	7.125	9.0

Dostal, Goff, and Hrdina[6] conclude that cholesterin stones "result from the absorption of bile salts by the diseased gallbladder with consequent precipitation of cholesterol."

In the authors' experiments reported in 1928[7] (Tables I and II) the obstruction of the cystic dust and foreign body cholecystitis were shown to be the essential etiologic factors in stone formation. The canine bladder deposited calcium carbonate about the human calculus (which was used as the foreign body in these experiments) in amounts apparently varying directly within the limits of the experiments with the length of exposure within the bladder. No attempt was made to produce a bacterial cholecystitis through the introduction

of bacteria for the surgical traumata and foreign body irritation inevitably set up inflammatory changes within the gallbladder wall. One should not

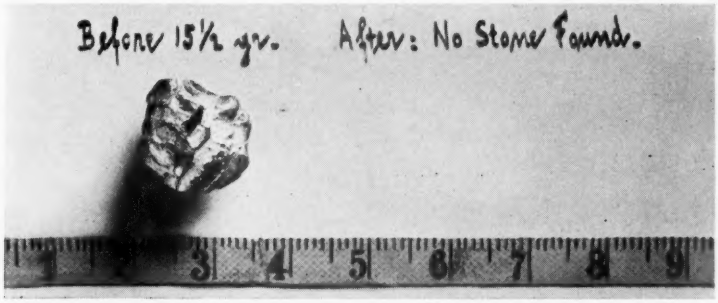

FIG. 1.—(See Table I.) Human calculus upon insertion in canine gallbladder. Disappeared in twenty-five days.

expect one of these bladders that has excreted calcium or has been exposed to irritation from stones to again become absolutely normal, nor should one

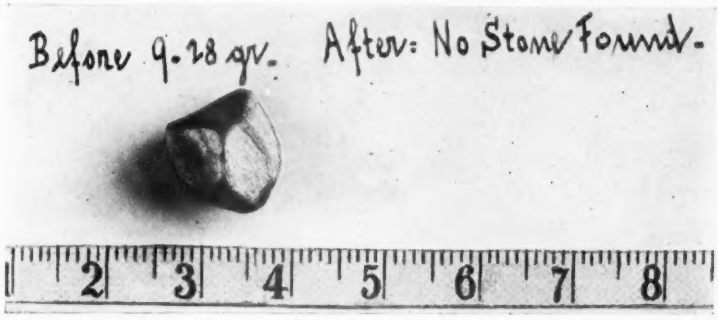

FIG. 2.—(See Table I.) Human calculus upon insertion in canine gallbladder. Disappeared in 126 days.

expect a potential stoneforming bladder to change into a bladder in which stones are absorbed. Repeated reoperations disclose stones previously observed but very rarely if ever absent from the gallbladders.

FIG. 3.—(See Table I.) Human calculus upon insertion in canine gallbladder. Decreased in sixty days.

This organic change in the bladder wall may not interfere with natural emptying under the roentgen ray. The active circulation of normal bile is

thought to be of greater value in preventing the reformation of concretions than a healthy bladder wall (Table III). To determine how much influence a badly damaged mucosa has on stone production the mucosae of four canine bladders were curetted, after which the bladders were sutured about human stones as in Table I. Note that in three out of the four animals the stones disappeared. In the single exceptional case (Table III), in which increase in weight of the calculus was observed after curettement of the lining of the bladder, the organ was atrophic and probably functionless.

TABLE III

Showing Effect of Curettement of Bladder Mucosa upon Human Gallstone

Exp. No.	Duration in days	Condition of bladder	Glands	Stone wt. gr. before	Stone wt. gr. after
93	7	Thickened	Enlarged	5.75	5.0
95	41	Normal (?)		7.875	0
A	31	Atrophic		6.0	7.5
100	31			7.125	4.125

Cf. loss in weight of bladder stone in Table I and Table III, indicating curettement of mucosa as possible negligible factor and circulation of bile as probable essential factor in the disintegration of a biliary calculus.

In the clinical cases above reviewed all the gallbladders had once been acutely inflamed, practically all had contained stones, many had become functionless as determined by the roentgen ray and failed normally to discharge bile. Recurrent cholecystitis and obstruction to the natural flow of bile (above reproduced in the experimental animals) statistically accounted for ten per cent of the 87 return "cholecystostomy" patients who subsequently developed new stones. Fistula formation probably prevented a higher incidence of recurrence by decompressing the inflamed bladders.

SUMMARY

(1) Of 500 gallbladder cases, 125 had cholecystostomy with 16 per cent mortality, 151 had cholecystectomy with two per cent deaths, and 224 had no operation with a fatality of 1.3 per cent.

(2) Of these 125 ostomies (1921–1932) 87 returned for follow-up examination. Of these 46 per cent remained symptom free. Of the remainder, 25 per cent complained of pain not attributable to the gallbladder. Hernia was observed in eight per cent. Fistula occurred in 11 per cent. Ten per cent developed recurrent stones.

(3) The improvement in the sugar tolerance was believed to vary directly with the subsidence of the biliary infection.

(4) Stones were found to disappear in normal canine gallbladders but to increase in size in the presence of obstruction and inflammation. The integrity of the mucous lining appeared to be a negligible factor in the disappearance of calculi.

(5) The recurrence of cholecystitis with impairment of the outflow of bile from the gallbladder were considered to be the essential causative factors of stone formation.

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HISTOLOGIC GRADING OF MAMMARY CARCINOMA

IN A SERIES FOLLOWED FOR TEN YEARS

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THE attempt to establish the prognostic significance of variations in tumor morphology seen under the microscope was first made by von Hansemann.[1] It was soon found that separate categories were necessary in classifying tumors of different organs. In the study of mammary carcinoma, the work of Greenough[2] revealed a parallelism between histologic evidences of tumor anaplasia and growth activity on the one hand and clinical results as estimated by the rate of cures at the end of five years' observation, on the other. White,[3] in his series of 100 cases, obtained results confirming the relationship found by Greenough.

However, many attempts to establish a definite prognosis in individual cases, from the histologic findings themselves, have proved unsuccessful. The reason for this nonsuccess rests on inability to determine by any means of clinical or operative examination the true extent of the disease in each case. Beyond doubt, most of those cases in which axillary metastases are found at operation or in the operative specimen have deposits of tumor cells in other nodes or in distant organs. Since such cases do not allow of surgical extirpation of the disease, their inclusion in a series of cases operated upon leads to confusion, and this confusion of cases pursuing their natural life histories and cases cured or helped by operation is probably the dominant, although accidental, element, which makes one series of cases different from another in which the same operative procedures were employed. The only group in which any uniformity of disease extent is probable is that of carcinoma in which careful search of the axillary nodes reveals no metastases. This group becomes relatively smaller after operation than before, and still smaller if the pathologic examination is painstaking and done by one familiar with the anatomy of the nodes of this region.

The original pathologic classifications of carcinoma of the breast distinguished medullary, adenocarcinoma and fibrosing (scirrhous) types. Classified on such a basis, it was found by Salomon[4] that adenocarcinoma was the most favorable group. Lindenberg[5] and later Boss[6] were unable to make this distinction and the latter found scirrhous carcinoma to have the best prognosis of the various categories. On the other hand, the unfavorable nature of scirrhous carcinoma appeared indicated by the analysis of 126 cases by Feist and Bauer.[7]

In Greenough's groupings, the original criteria of von Hansemann were used, rather than mere subdivisions based on cell patterns and fibrous tissue

content. He placed emphasis on those morphologic features connected with cellular differentiation and function, namely, grouping in acinus formation and content of secretion. Such cells were well differentiated and therefore to be considered of lesser malignancy. Other factors considered by Greenough were regularity in size of cells and nuclei and in the chromatin arrangement in the nuclei, and the frequency of mitotic figures.

Instead of the above criteria, MacCarty[8] believed greater importance was attached to the degrees of fibrosis, hyalinization and lymphocytic infiltration as factors tending toward encapsulation and possibly defensive reaction, comparable to that seen in tuberculosis.

Heuper[9] combined all these histologic factors and added to them such minutiae as the nucleocytoplasmic ratio, the vascularity of the stroma, and the number of "pencil" cells, considering in all 20 separate features as having some weight in the prognosis.

Recent surveys of case groups have tended to throw doubt on the significance or value of many of the factors previously considered important. Evans[10] found that fibrosis and lymphocytosis could not be made to show any correlation with eventual outcome in his series. He could likewise find no significance in a casual estimate of the frequency of mitotic figures. He could find some significant correlation with prognosis only in regard to two factors, tubule formation and cell regularity of shape and size. The cases with uniform cells with definite tubular arrangement were obviously more favorable in outcome.

Haagensen[11] studied exceptionally favorable material in a series of 164 cases and found that, analyzed for each one of 15 histologic details, the ones which bore no statistically convincing relationship to outcome were: (1) Hyperchromatism of nuclei; (2) fibrosis; (3) hyaline degeneration; (4) lymphocytic infiltration; (5) plexiform arrangement. The factors having significant variation in favorable and unfavorable cases, he found were: (1) Papillary arrangement; (2) comedo formation; (3) adenoid arrangement; (4) variation size and shape of nuclei; (5) number of mitotic figures; (6) gelatinous degeneration.

Statistics of this Series

This study was made on a series of cases of carcinoma of the breast in which operative radical removal of the breast had been performed by the Halsted method or a modification of it and a postoperative record was available. The cases were obtained from those operated upon at Roosevelt Hospital between 1915 and 1925 and therefore a postoperative history of from ten to 21 years was available. These records had been assiduously maintained by Dr. William Crawford White, without whose assistance the study would have been impossible.

There were 124 cases falling into the period and having both sufficient postoperative data and tissue slides for microscopic grading. Of these cases the age at time of operation ranged from 29 to 77 years. Seventeen cases of

women of 40 years or less appear in the series. Four of these (24 per cent) were well and free of disease for periods of from 10 to 21 years after operations. One case died 12½ years postoperatively of unknown cause, and another six years postoperatively of recurrence. The total group showed 18 or 14 per cent, cured after this prolonged period of follow up. There remain also a group of eight in whom no clinical evidence of tumor was present at the time of death six to 14 years postoperatively. If these are added to the cured cases, the percentage of cure is 20 per cent.

The method of study employed in this analysis was as follows: The available microscopic slides were examined as a group, without reference to information as to the clinical outcome. A separate grade from one to three was ascribed to each of those factors in histologic structure to which credit for influencing rapidity of tumor growth has been assigned by various authors. These were nuclear size, nuclear constancy or variability of size and form, regularity of adenoid cellular grouping, number of mitotic figures, presence of papillary structure, number of lymphocytes infiltrating the tumor, extent and density of fibrosis, amount of intracellular secretion and occurrence of comedo formation.

The cell sizes were not considered reliable because of difficulties due to thick sections and variable dehydration. The nuclei were therefore used as a better criterion. A representative group of nuclei was traced by camera lucida from each slide. These drawings were then used to assign each case a grade as to nuclear size and another as to nuclear variability. The numbers used throughout were in ascending scale of probable malignancy, and therefore the small and uniform nuclei were graded one and the large and irregular ones three. The use of camera lucida drawings was thought to furnish a check on personal variations in opinion. Where the cells varied from section to section, the practice was to use the looser portions or the cells invading fat, rather than those buried in dense fibrous stroma. After all the slides had furnished representative groups of nuclei, a decision was reached as to which belonged to the smallest and which to the medium and largest groups. Likewise, since 8 to 15 nuclei had been drawn for each slide, it was possible to decide on the relative constancy or irregularity of nuclei, using the other drawings as a check on each decision.

The content of secretion was not estimated by special staining, since the original tissue had all been fixed in formalin. There is still considerable question whether the mucicarmine stain is as valuable as claimed by Delbet.[12] Besides the absence of a series of cases in which it has been done and the relation to outcome compared with the relative degrees of secretion observed, theoretically alone it is discouraging to realize that glycogen frequently stains with mucicarmine and has caused considerable confusion thereby in the study of the glandular epithelium of the endometrium. In this study the presence of vacuoles of secretion, of intracellular and intratubular hematoxylin staining material and of clarity of cytoplasm were noted as signficant of varying degrees of secretion.

Mitotic figures were estimated by counting the number in ten high-power (x400) fields in different parts of the slide. If many fields showed none, the case was grouped as one. If each field showed several, the grouping was three.

The arrangement in glandular tubules was expressed as greatest (1) when the predominant mass of the tumor had cells grouped about a lumen, and as medium (2) when such arrangement was seen in some foci while many solid nests and narrow strands were also seen. When only the latter form of growth was found, the classification was Grade III.

The intensity of fibrosis and of lymphocytic infiltration was graded from one to three, giving the greatest degree of each the value one, according to the idea that they were defensive factors.

After this scheme had been completely fulfilled, the case histories were filled in opposite each case number, giving the years of survival and data as to recurrence or metastases. It was now possible to tabulate the cases in groups, three grades for each of the following factors: nuclear size, nuclear variability, mitosis, degree of lymphocytic infiltration and degree of fibrosis. Only two grades were found practicable in regard to adenoid arrangement, since there were so few cases with Grade I tubule formation, and likewise only two groups for secretion were finally achieved. Papillary structure and comedo arrangement did not occur often enough (five cases in all) to furnish separate groups. These factors were, however, weighed in the combined grading discussed below.

Table I represents the total group, showing how the occurrence of axillary metastases varied with the grades of the several histologic criteria. The striking positive feature is the definite preponderance of axillary metastases in the group graded three compared with that graded one and two as to adenoid arrangement. It would seem that the tumor with well formed tubules is more favorable on account of its slowness to metastasize and the frequency with which at operation no axillary metastases are to be found. All other criteria fail to show such a definite correlation with the percentage of metastatic involvement.

TABLE I

Percentage of Axillary Metastases Found in Pathologic Examination of 124 Cases, Graded by Separate Criteria

	Grade I		Grade II	Grade III
Nuclear size	65%		64%	75%
Nuclear variability	59%		70%	77%
Adenoid arrangement		49%		80%
Secretion		62%		71%
Mitosis	64%		73%	73%
Fibrosis	74%		74%	60%
Lymphocytes	63%		71%	73%

The entire group revealed an incidence of positive axillary nodes in 69 per cent of cases. It is evident from the Table that grading by each of the criteria employed reveals an increased incidence of axillary metastases in the higher grades, except in the grading according to fibrosis. The greatest variation and positive coincidence of grading and metastases are found in the subdivisions on the bases of adenoid arrangement. The next greatest are noted in the grading by variability of nuclei. All other criteria, except degree of fibrosis, show some positive coincidence but not of such marked degree.

The second method of analysis was a comparison of groups graded by the same criteria restricted to cases in which no axillary metastases were found by pathologic examination. The clinical outcome in such cases should be dependent upon the growth activity of the tumor itself, rather than upon unknown extensions of the disease as is the case with those having axillary metastases. Table II reveals the results of such an analysis. The great weakness is the paucity of the material. A substantially longer life and a greater percentage of ten year cures are found in the cases graded one as to nuclear variability, nuclear size, secretion, lymphocytic infiltration and mitoses. Grade II was found intermediate between one and three except in the case of lymphocytic infiltration to grading by degree of fibrosis, the Grade I appeared paradoxically unfavorable.

TABLE II

Thirty-nine Cases Without Axillary Metastases Graded by Separate Criteria Showing the Years of Survival of the Dead and the Percentage of Living Cases after Ten Years

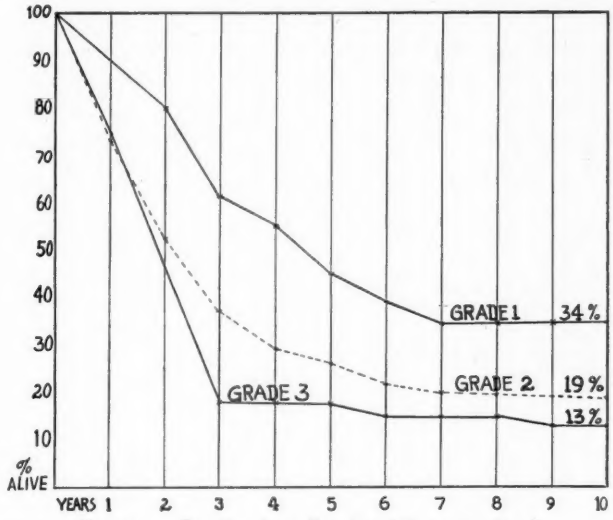
	Grade I	Grade II	Grade III
Nuclear size	4.4 yrs.—64% living	3 yrs.—53% living	3.2 yrs.—39% living
Nuclear variability	5.2 yrs.—73% living	3 yrs.—45% living	2 yrs.—37% living
Adenoid	4 yrs.	52% living	2.5 yrs.—50% living
Mitosis	3.9 yrs.—50% living	1.5 yrs.—73% living	3.2 yrs.—17% living
Secretion	5.7 yrs.	56% living	2.3 yrs.—48% living
Lymphocytes	4 yrs.—73% living	3.3 yrs.—31% living	3.3 yrs.—46% living
Fibrosis	2.1 yrs.—33% living	3.4 yrs.—53% living	4.1 yrs.—50% living

In an effort to unify the information available by the use of the criteria found valuable in the two analyses above, it was decided to establish a combined grading for each case. The grades for nuclear size, nuclear variability, adenoid arrangement and mitosis were added together. If the presence of secretion had been detected, this total was reduced by one. If there was comedo or papillary arrangement, the total was reduced by one for each such factor. This gave a possibility of totals from less than four to 12. Grade I was taken to be any combined total of less than seven, Grade II, from seven to nine, and Grade III, above ten. In this way it was felt that the decisive histologic features were all given some rôle in the establishment of the grade, although their relative values remained unknown and indeterminable.

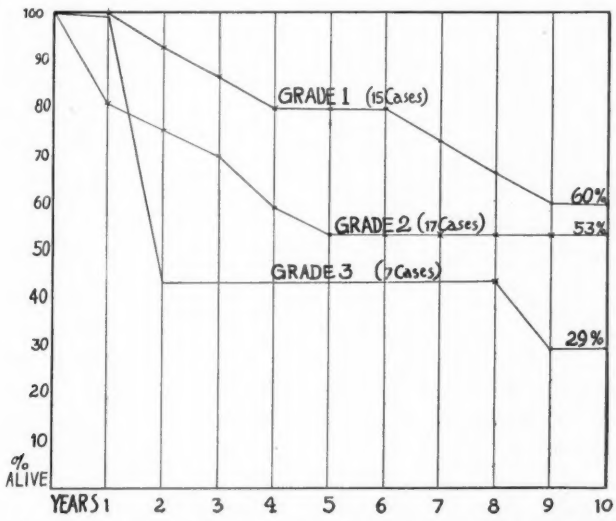
Graph I shows the results of this method of grading, with a ten year

clinical follow up. The ten year cure rate varies with grading; 34 per cent for the Grade I group, 19 per cent for Grade II, and 13 per cent for Grade III.

In the cases without axillary metastases, the ten year cure rate is seen by Graph 2 to show for Grade I, 60 per cent; Grade II, 53 per cent; and Grade III, 29 per cent.



GRAPH 1.—Results of grading in whole group (124).



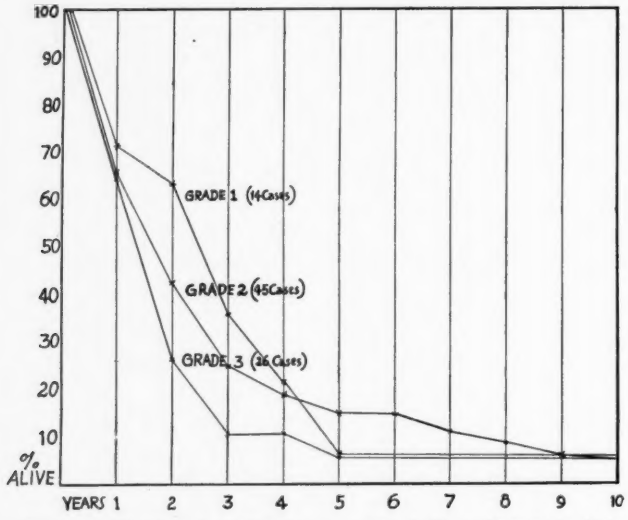
GRAPH 2.—Results of grading in cases free of Axillary Metastasis (39).

In the cases with axillary metastases, the ten year cure rate for all grades is 7 per cent (Graph 3) but the length of life after operation is greatest in Grade I and least in Grade III. This uniformity in eventual outcome is confirmatory of the assumption that the case with axillary metastases usually has

extensions of the tumor beyond the zone of operation, and the outcome is dependent on this invisible factor. However, as Haagensen[11] points out, the grades show a relative difference in these cases where operation has been unavailing, just as it does in the early cases where high percentages of cure are found.

CONCLUSIONS

A series of 124 cases of mammary carcinoma treated by radical operation and followed ten years or longer is analyzed by histologic criteria. A definitely lower incidence of axillary metastases at the time of operation was noted in the cases with Grades I and II adenoid arrangement, compared with those growing in solid cords and masses (Grade III). This fact appears to account



GRAPH 3.—Results of grading in cases with Axillary Metastasis (85).

for the previously recognized favorable clinical aspect of the adenocarcinoma. Degrees of fibrosis appeared to exert no influence. Marked lymphocytic infiltration (Grade I) was noted in a group which had a slightly better clinical result than that without this feature. The most significant correlations of clinical outcome and grading appeared in respect to adenoid arrangement, nuclear constancy, nuclear size, mitoses and secretion. The few cases in this series with papillary and comedo arrangement were found to have had a more favorable course.

By a method of combining the information concerning each of the criteria employed, a grading of each case was achieved which shows a definite statistical parallelism with the percentage of ten year cures. This is found to depend on the incidence of cases without axillary metastases. The cases with metastases show uniformly poor ten year results, probably because of the advanced stage of the disease at the time of treatment. Since such cases outnumbered the favorable ones more than two to one in this series, it becomes

evident that the invisible extensions of carcinoma not recognizable at the time of operation form the major controlling factor in the prognosis of the individual case. The histologic analysis indicates nevertheless a relatively slower or more rapid clinical course according to grade of tumor.

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SYMPOSIUM

ON

CANCER OF THE BREAST

AT

THE FIFTIETH ANNIVERSARY OF THE MEMORIAL HOSPITAL

NEW YORK, N. Y., MAY 25, 1934

Chairman, FRANK E. ADAIR, M.D.

THE EARLY DIAGNOSIS OF BREAST CANCER. ROBERT B. GREENOUGH, M.D., Boston, Mass. President, American College of Surgeons.

BIOPSY IN BREAST LESIONS. JOSEPH COLT BLOODGOOD, M.D., Baltimore, Md. Professor, Clinical Surgery Johns Hopkins Medical School.

THE CLASSIFICATION OF MAMMARY CANCER. JAMES EWING, M.D., New York, N. Y. Director of the Memorial Hospital.

SURGICAL PRINCIPLES IN CANCER OF THE BREAST. DEAN LEWIS, M.D., Baltimore, Md. President, American Medical Association.

THE VALUE OF PREOPERATIVE IRRADIATION IN BREAST CANCER. FRANK E. ADAIR, M.D., New York, N. Y. Executive Officer of the Memorial Hospital.

EARLY DIAGNOSIS OF CANCER OF THE BREAST

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FOR the purposes of this discussion we may define "Early Diagnosis of Cancer of the Breast" as the recognition of the disease in its early stages of development, while it is still confined to a single area, in the vicinity of its point of origin, and before it has extended either through the lymphatics, the blood vessels or by infiltration to regions beyond the borders of the mammary gland. Since the rate of growth and of extension of cancer of the breast varies within such extraordinarily wide limits, the factor of time, whether measured in weeks, months, or years, is of relatively little significance in the prognosis unless considered in its relation to the other conditions existing in the individual case. In the 1924–1926 series of cases, recently reported by Simmons, Taylor and Wallace from the Massachusetts General Hospital, 94 cases of *less* than six months' duration gave 41, or 43.5 per cent of five year cures; while 49 cases of *over* six months' duration gave 21, or 43 per cent of five year cures.

The significant feature in early diagnosis, therefore, is not so much the duration of the disease in point of time, as the degree of extension of the disease which has occurred during that period. Taken in this sense, few of us will deny that "early diagnosis" is by far the most significant factor in the prognosis of cancer of the breast, and a brief discussion of this subject may well be justified.

The classic and accepted criterion for the diagnosis of cancer of the breast demands that the epithelial cells of the breast gland shall be shown to have infiltrated beyond the basement membrane of the ducts, or acini, and be identified in the surrounding tissues. In our present state of knowledge, and in spite of opinions expressed to the contrary, I believe that it is wise to adhere to this criterion, and to regard the anaplastic morphology of single cells, or of cells within their normal structural confines, as evidences of hyperplasia, precancerous if you will, but not as justification for the diagnosis of cancer.

For this reason we are forced to regard the small single nodule of cancer in the breast as the primary tumor. From our knowledge of the long period of time required for the production of artificial cancer, we may well believe that the development of such a nodule is probably a matter of years, rather than months. In that sense, therefore, the early diagnosis of cancer of the breast from the point of view of time may be an impossibility, but early diagnosis from the point of view of extension of the disease is an actual fact, and a most important one. In clinics where successive series of cases are reported in a uniform manner, the percentages of early cases appear to be

increasing slowly and surely with the steady advance in the education of the public and of the medical profession.

In 1914, at the Massachusetts General Hospital, only 26 per cent of the operable cases were in the early group in which the axillary glands were found not to be involved on pathologic examination, while 74 per cent showed positive axillary involvement. In the series ending in 1926, the percentage of axillary involvement had dropped to 60 per cent, and 40 per cent of the cases were in the early local stage of the disease. This, I believe, is a clear indication of the value of public education.

The symptoms of advanced cancer of the breast are all too familiar to need discussion here. The earliest recognizable symptom is almost invariably that of a lump or tumor in the breast. Lee recorded that in six per cent of his cases only was pain noted as the first symptom which attracted the patient's attention and led to the discovery of the tumor. Such a single tumor, whether painless or tender, may be cancer or it may be many other things, some of which are recognizable and others not. In my own experience the first symptom which can be considered in any way pathognomonic of cancer is the loss of mobility of the skin over the tumor. This sign is best elicited by gentle pressure designed to move the breast upward or outward on the chest wall. There are, however, exceptions even to this rule; for traumatic fat necrosis, plasma cell mastitis, chronic abscess and infected cysts, especially when situated toward the mid-portion of the breast, may all cause loss of mobility of the skin. Variations of this phenomenon, which is attributable to the shortening of the ligaments of Sir Astley Cooper, are atrophy of the superficial fat, flattening, and in more advanced cases dimpling of the skin, retraction, elevation, or other displacement of the nipple from its normal position, and diminution of the size of the whole breast.

The discharge of clear or brownish fluid from the nipple, and even that of pinkish or bloody fluid, is to be regarded, in my opinion, not primarily as a symptom of cancer, but as evidence of a chronic inflammatory process in the ducts of the mammary gland with more or less hyperplasia of the ductal epithelium, even to the extent of the development of a papillary cystadenoma. Such conditions must, of course, be regarded as of precancerous significance, but the sympton of discharge from the nipple is usually found to have been present for a considerable time before the development of a tumor can be recognized. It has been suggested that microscopic examination of this discharge may make possible the diagnosis of cancer. (I have never seen this accomplished.)

The more common conditions to be considered in the differential diagnosis of cancer of the breast can be classified somewhat as follows:

(1) Benign tumors of the adenofibroma and myxoma group and adenosarcoma.

(2) Nonintrinsic tumors such as lipoma, angioma, lymphangioma, neuro-

fibroma and varieties of sarcoma, including lymphosarcoma, which may occur in the connective tissues of the breast as in other regions of the body.

(3) The chronic inflammatory processes, such as tuberculosis, syphilis and actinomycosis.

(4) The acute, subacute and chronic manifestations of lactation mastitis, including plasma cell mastitis.

(5) Traumatic fat necrosis, deep hematoma and other results of trauma.

(6) The wide range of pathologic conditions which have been described under the comprehensive term of chronic mastitis, including nodular mastitis (mazoplasia), cystic disease (cystopherous hyperplasia), and papillary cystadenoma (intracystic papilloma). Such lesions may be accompanied by acute inflammatory symptoms or may be subacute or chronic.

Many of the above conditions have such characteristic signs and symptoms that the diagnosis of their presence can be made with practical certainty, on careful consideration of the patient's history and the direct physical examination. Many of these diseases, however, are also very definitely recognized as of precancerous significance, and the real difficulty of diagnosis lies as a rule not in the failure to recognize the existing noncancerous condition, but in the total inability of the physician to be able to assure the patient by any form of external examination, unsupported by a biopsy, that cancer is not present also.

If we can detect no physical abnormality in the breast, we can indeed report that we find no evidence of disease; but in the presence of any mass or tumor whatever, the possibility of cancer being already present must be considered, either as a natural development of the disease in question, or independent of that disease entirely, and merely concealed by the physical presence of the concomitant lesion.

If we accept this view of the situation, we must be prepared to consider every tumor of the breast of a woman over 20 as involving the possibility of cancer, and in all cases where the positive diagnosis of cancer is not readily made from physical examination, we must so conduct our operative exploration as to obtain certainty of diagnosis by biopsy, without, at the same time, if cancer is present, diminishing in any way the chance for cure, to which the patient is entitled. This, I may say, in the past has not always been done, and is not always done today. Some of the most tragic instances of failure to cure cancer of the breast in early and favorable cases are due to the fact that operation is undertaken for a supposedly benign condition, and the presence of cancer is recognized only after the tissues have been widely contaminated with living cancer cells.

The most recent additions to our resources in the way of diagnostic methods are transillumination, and the "soft part" radiographic examination of the breast in profile. Both methods may be said to be still on trial, and neither has as yet proved itself of such conspicuous value as to weigh heavily in the scale unless the findings are confirmatory of the diagnosis already suggested by the physical examination. In a certain number of cases, however,

each of these methods may be of the greatest service, and a wider employment of them is greatly to be desired.

Another method of using the roentgen ray, namely, as a therapeutic test, has been employed in certain instances. As to the value of this method I cannot speak; I have not tried it and cannot bring myself to feel that it is justifiable. The widely recognized lack of radiosensitivity of breast cancer alone would seem to me to make this procedure a dangerous one on account of the delay and difficulty involved in obtaining a decisive conclusion. We must not forget that the cure of cancer of the breast is still a question of surgical intervention, and the earlier in the course of the disease that operation is performed, the better are the results. We must not forget, also, that in most cases it is quite as important to the patient to be certain that cancer is not present, as it is to confirm a diagnosis of cancer already to be presumed from the physical examination.

The real problem involved in the early diagnosis of cancer of the breast is, therefore, to determine that method of performance of a biopsy which will permit a gross as well as a microscopic examination of the tissues under suspicion, without endangering the patient's chance of cure by surgery if cancer is present. Such a method of examination must give an adequate exposure of all of the abnormal tissue, in order that the patient who is suffering from a benign lesion may be given complete assurance that cancer is not present in her breast.

The radiographic examination of the chest and of the bones is an essential part of the physical examination of any case of tumor of the breast, where the possibility of cancer is to be considered. For this purpose films of the chest, spine, pelvis and shoulder girdle, including the upper ends of humerus and femur, are required. The recent observations of Dresser would appear to make it advisable to include also the examination of the skull.

The physical examination of the axilla, important as it is in early cases, is often inconclusive. This is due in part to the varying depths of subcutaneous fat in different patients, but partly also to the fact that conditions other than cancer may be responsible for the enlargement of axillary lymph nodes to the extent of making them readily palpable. In the three year series reported from the Massachusetts General Hospital ending in 1923, 16 out of 50 cases (32 per cent) in the IA group were recorded as having enlarged glands in the axilla; but on pathologic examination were found to be free from cancer, while in 24 out of 111 cases where the glands proved to be involved, no enlargement could be detected on clinical examination. Under these circumstances the clinical examination of the axilla must be acknowledged to be somewhat inconclusive.

The methods of operative exploration now in use include (1) Direct incision (or excision) of the tumor. (2) Simple amputation of the breast. (3) Aspiration. (4) Punch-trocar method of biopsy. The first consideration is that the biopsy and the operation required should be included in the same

operation. The use of preoperative radiation before biopsy is a precaution widely employed to diminish the danger of an exploratory operation. Such a procedure is amply supported by logic, but I know of no statistical evidence to support this practice. The patient should be in the hospital and should be prepared for a radical mastectomy. A direct incision may be made into the tumor or (if the tumor is small and circumscribed) the tumor itself with a wide margin may be excised. The wound is then immediately packed with formalin (10 per cent) gauze, and the pathologic examination made. If positive for cancer, the exploratory wound is closed, over the formalin gauze; instruments, gloves and dressings are discarded, the operative field is again prepared, and with a new layout the radical operation is performed. If radical operation is not required, the formalinized tissues are excised and the operation indicated is performed. The electrosurgical unit with its cutting and coagulating current can be employed to advantage in performing a biopsy of this nature, especially where excision of the tumor is deemed advisable. It must not be forgotten, however, that cooked tissue does not lend itself well to pathologic examination.

In the years 1918–1926 at the Massachusetts General Hospital, exploratory operations by direct incision or excision of the tumor were performed in 42 cases, with 21, or 50 per cent, five year cures. During this period 310 operations were performed without exploration with 104, or 33 per cent, five year cures. These figures are, of course, not conclusive evidence of safety, for it is usually, though not invariably, the early cases which require an exploratory incision, but the results so nearly approach the results in all of the early and favorable (IA) cases (62 per cent) as to suggest that the exploration diminishes little, if at all, the patient's normal expectation of a successful result.

There are certain cases of supposedly benign lesions, such as cystic disease, which involve so large a portion of the gland that an adequate gross and microscopic examination demands the removal of the whole breast. In such cases the severance of the lymphatic channels between the breast and the chest wall undoubtedly involves danger of contamination of the wound with cancer cells in any but the earliest cases in which cancer is present. In such operations the electrosurgical unit is usually to be preferred to the scalpel. In the nine year period above mentioned, 23 simple amputations of the breast were done, in which cancer was discovered on pathologic examination, and the radical operation was then immediately performed. Of this number, 14 were five year cures (61 per cent). This was before the time of general use of the electrosurgical unit. It must be admitted, therefore, that this method is not always so dangerous as it has been sometimes held to be.

During this same period seven additional cases of cancer were explored through the Thomas axillary incision under a presumptive diagnosis of cystic disease. In all of these cases the radical operation was completed immediately,

and five of the seven (71 per cent) were five year cures, again a suggestion that the unexpected discovery of cancer, in a supposedly nonmalignant breast, need not be disastrous to the patient if proper cauterization, by heat or chemicals, is employed, and the radical operation immediately completed.

A summary of the above figures shows that 72 cases of biopsy gave 53 per cent of five year cures; as against 310 cases of radical operation without biopsy, which gave 33 per cent five year cures.

My own experience with the aspiration and the punch-trocar method of biopsy is very limited, and I must leave their discussion to others more familiar with their use. I am impressed, however, with two points in relation to these methods: (1) the difficulty in being sure that the tissue removed actually comes from the suspected area in the breast; and (2) the difficulty in securing sufficient tissue to permit a positive diagnosis. In any case, one must assume that a negative finding can be held as of little value, and since the safety of the patient requires the certainty that cancer is not present, in many such explorations the purpose of the biopsy would not be obtained.

In conclusion, therefore, the items I would submit for discussion are as follows:

(1) "Early diagnosis" of breast cancer means early in the course of the disease, rather than early as measured by the duration of the symptoms in point of time.

(2) The first symptom of cancer of the breast is usually a lump in the breast.

(3) In the absence of distinctive symptoms in addition to the lump, such as loss of skin mobility, retraction and deformity, or enlarged axillary nodes, an exploratory operation is usually a necessity.

(4) This exploration must be conducted in such a way as not to rob the patient of her chance of cure if cancer is present.

(5) It should permit such an exposure of the tissues, for gross and microscopic examination, as will make it possible to assure the patient positively that she has or has not cancer.

(6) The use of preoperative radiation, and the employment of the electrosurgical unit, provide additional safeguards in cases where direct biopsy is considered to be dangerous.

(7) Delay between exploration and radical operation in cancer of the breast is to be avoided, and the exploration should not be done unless, and until, all arrangements for competent pathologic examination by frozen section and immediate radical operation are available.

(8) Exploration by direct incision is the method to be recommended for general use. In some few cases simple amputation is required.

(9) Operations on supposedly benign breast lesions should be so conducted that, if cancer is found to be present, the patient shall not thereby be deprived of her chance of cure.

BIOPSY IN BREAST LESIONS

IN RELATION TO DIAGNOSIS, TREATMENT AND PROGNOSIS

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THE chief danger of biopsy in breast lesions today lies in a mistaken diagnosis which may lead unnecessarily to the removal of the breast or to the complete operation for cancer. When the surgeon has the benefit of a well-trained pathologist in the operating room, a biopsy is the least dangerous method of determining the benign or malignant nature of the breast lesion. There was presented before the Surgical Section of the American Medical Association at Cleveland a lantern-slide demonstration of the four types of breast tumors which can be excised by cutting through uninvolved breast tissue without seeing the neoplasm and closing the wound without interfering with the symmetry of the breast. These four types are: A distinctly benign lesion; and a border-line lesion; a distinctly malignant lesion; and a Grade IV type of acute carcinoma.

For the benign and the border-line lesion, I urge that after excision of the lump the wound be closed and that the patient receive immediately deep roentgen ray therapy over the axilla and that from five to ten days later the irradiation be continued over the breast and over the wound. During this time sections of the border-line lesion should be submitted to two or more of the most experienced surgical pathologists in breast tumors. When these authorities differ, or agree as to benignancy of the growth, no further intervention is necessary. If the authorities agree on malignancy, then the operator has the choice between depending upon irradiation alone or performing the complete operation for cancer. Apparently the majority of operators, pathologists and radiotherapeutists prefer the complete operation in cases in which the pathologists unanimously agree that the growth is malignant.

An exhaustive consideration on "biopsy" which was presented by me before the Southern Surgical Association (Amer. Jour. of Surg., vol. 24, p. 331, May, 1934), and subsequent dissertations confirm previous statements. There are two excellent reviews on biopsy which give the literature from the time of Virchow to date (Helwig: Arch. of Path., vol. 14, pp. 17–554, October, 1932) and McGraw and Hartman of the Henry Ford Hospital (J.A.M.A., vol. 101, p. 1205, October 14, 1933).

In the discussion of my paper before the Southern Surgical Association, the remarks of Dr. Bradley L. Coley, of the Memorial Hospital in New York, on aspiration biopsy on bone tumors is reported in considerable detail. This method has many advantages. It can be done anywhere under local anesthesia, but the operator must understand his technic. It seems to be without danger. The greatest difficulty is for the pathologist in the interpreta-

tion of the nature of the pathologic process largely by the morphology of the cells. These stained cells can be sent to pathologists who have had greater experience in their interpretation, and if this proves equally satisfactory, aspiration biopsy will ultimately take the place of excision of the nodule or excision of a piece of tissue. From my experience up to date in border-line tumors, I am not yet convinced that aspiration biopsy will be able to compete with the complete excision of the nodule and the examination of immediate and permanent sections. In the Memorial Hospital, with their special training, their negative results, according to Coley, are about 25 per cent.

This paper will be devoted to the discussion of three recent observations on breast tumors which were rather difficult to diagnose. One ultimately proved to be a comedo-adenocarcinoma without involvement of glands. In this case I did not have the courage of my convictions and, after excising the lump, rather a large one, and studying the frozen sections, I performed the complete operation for cancer without any restrictions. The other two cases proved to be benign blue-domed cysts. One felt so much like cancer that after a negative aspiration biopsy I performed the complete operation for cancer. Had I excised this palpable clinically malignant tumor and then bisected the mass, I should have exposed a typical blue-domed cyst and saved the patient from the complete operation for cancer. In the second case of blue-domed cyst which was clinically almost as suggestive of malignancy as the first, I excised a mass larger than in the first and, after removal and bisection, found two blue-domed cysts, the overlapping of which had produced a dark shadow on transillumination.

It is very important to state here that the finding of this comedo-adenoma after the excision of a doubtful lump in the breast, and its recognition in gross and frozen sections, led to the complete operation, because I knew that there are two types of this typical comedo-adenomatous tumor. In one, the less frequent form, the glands are not involved, and it seems justifiable to restrict the operation to the removal of the tumor, while in the second type there are areas of microscopic cancer mixed with the comedo-adenoma, and in this group the glands are involved in about one-half of the cases. In the last case of comedo-adenoma discussed in this paper, the area involved was too large to make complete sections of and exclude evidences of malignant parts. I could, however, have closed the wound and immediately irradiated the axilla while making complete sections. But the area which I had excised, including the nipple, was so large that a normal and symmetrical breast would not have been preserved.

This simply shows how difficult it is for one whose training has been surgical as well as pathologic to force himself to perform a restricted operation for a malignant tumor of the breast. I agree absolutely with the statement of my colleague, Dr. Dean Lewis, which he made during the discussion of breast tumors in the meeting in the Memorial Hospital May 25, that there

should be no restriction if an operation is performed for an operable malignant tumor of the breast.

CASE I.—(Pathol. No. 53384.) *Diagnosis.*—Two blue-domed cysts in chronic cystic mastitis. Clinically doubtful case. The palpable tumor slightly larger than a 25 cent piece transilluminates slightly darker than usual for the blue-domed cyst, and yet not so dark as one would expect of a solid tumor, benign or malignant. (Fig. 1.)

There was nothing in the clinical history particularly helpful. The patient was a married woman, aged 40; no children or miscarriages. Her last menstrual period was about three weeks before she was examined. She first observed that both breasts have been larger than normal in the past six or eight years, since she has gained 30 pounds in weight. On inspection, the breasts and nipples were normal, except the increase in size. In the mid-zone of the upper hemisphere there was found on

FIG. 1.—(53384.) Photograph of excised mass from breast, clinically doubtful. After excision exploration showed two benign blue-dome cysts surrounded by adenomatous breast tissue. (See Fig. 2.)

transillumination a darker area, but not so dark as the usual solid tumor. One could make it out, however, and it was in distinct contrast with the clear transillumination of the right breast and the remainder of the left breast. This dark area was the only palpable area in either breast. It was freely movable and felt like an adenoma buried in breast tissue. Remember, we palpated only one tumor and found at operation two cysts. My associate, Doctor Stewart, thought that the tumor fluctuated a little. A tumor of this kind must be regarded as doubtful, aspirated or explored. In view of the fact that it was of five months' duration and there were no other areas in either breast, and the patient was 40 years of age, I decided to aspirate and then explore in the operating room, with the patient prepared for the complete operation for cancer. The patient consented to whatever was necessary.

I decided against aspiration in favor of excision of the lump. As she had a large breast we could excise a fairly large area of tissue without producing any deformity after closing. In cutting through breast tissue we exposed a larger number of elevated pink dots of parenchyma. The frozen sections of this showed chronic cystic mastitis. (Fig. 2). This finding, of course, does not exclude cancer, but it favors the palpable tumor's being a blue-domed cyst. In cutting through the breast tissue between the

nipple zone, we divided numerous dilated ducts just as typical of chronic cystic mastitis as the numerous pink elevated spots. Sections showed dilatation of ducts without comedos or papillomas. This finding also would not exclude a cancer. The specimen was removed and bisected; cutting through the breast tissue first exposed a blue-dome (Fig. 1), then nicked a thin-walled cyst, and cloudy fluid escaped; the wall was smooth; there was no papilloma. Palpating the remainder of the mass, another palpable lump was felt which on exploration proved to be a second blue-domed cyst. The surrounding breast cut through to expose these two cysts was identical with the breast cut through in excising this mass. We had not recognized the second lump until we had explored the first lump. I feel confident that the dark shadow in the transillumination in this case was due to the fact that the cysts were superimposed. I have demonstrated this

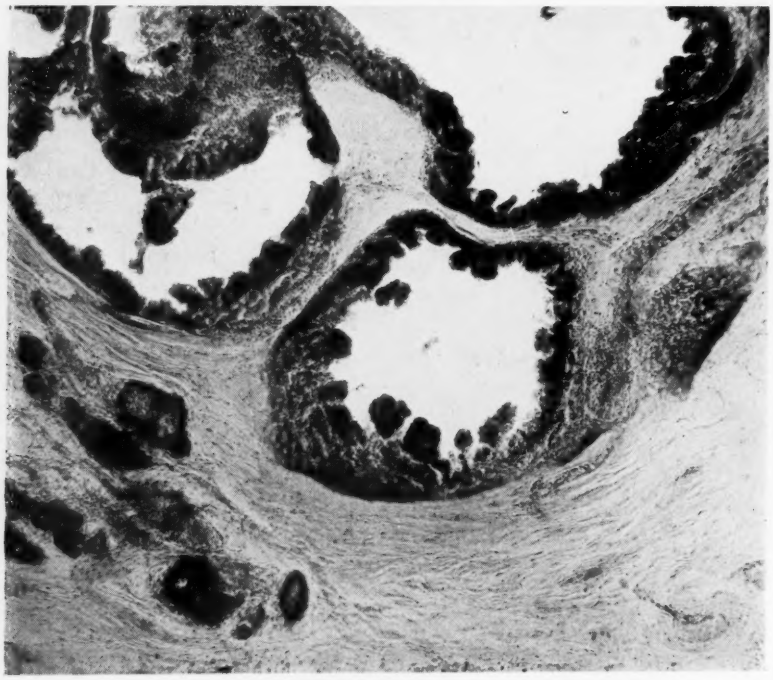

FIG. 2.—(53384.) Section of an adenomatous area in the breast tissue above the blue-dome cyst in Fig. 1.

possibility before. Perhaps, when I have had more experience with aspiration biopsy, I will save more patients from an operation of this character which often means anesthesia and a week in the hospital. But, at the present time, there seems no other way of getting a proper biopsy in blue-domed cysts which, in some ways, are clinically doubtful or even clinically malignant. In this instance a surgeon trained in gross pathology will be certain of his diagnosis from the naked-eye appearances, but there is no question that frozen section confirmation is helpful and, if possible, should be part of the operative diagnostic procedure.

The second case will not be described in detail. In this instance the palpable tumor transilluminated dark and felt like cancer. All my associates and the internes on the surgical service were of the opinion that it felt like cancer. Yet there was no fixation or retraction of the nipple, but the mass palpated like a malignant tumor. It had the typical hard and irregular

surface. I know that in 1 or 2 per cent of blue-domed cysts there have been retracted nipples, dimpling of the skin, or, on palpation, a peculiar sensation so common in malignant tumors. In this case I thought that the palpable mass fluctuated, but very frequently I have thought I have observed fluctuation and found at exploration a small cancer buried in edematous fat. There is no question that the clinical diagnosis of breast tumors is becoming more and more difficult as their duration is shortened, and in many clinics today breast tumors of one month or less duration are becoming the most common tumors observed.

My experience now over a number of years in the employment of transillumination of the breasts is convincing me that it has an equal value with palpation. The most important part about transillumination is a really dark room. The light is of lesser importance. Two or three small pocket electric pencil lights are sufficient. As transillumination is just as efficiently done with the patient standing up as sitting up, a dark closet will answer. The advantage of transillumination on the examining table is that it is better done with the patient lying down as well as sitting up, and this allows transillumination to be employed in both positions.

FIG. 3.—(53498.) Gross appearance of typical comedo-adenoma of breast excised for microscopic examination. (See Fig. 4.)

In the second blue-domed cyst case, the patient was prepared for the complete operation on the operating table, and I aspirated the palpable lump three times, and was able to obtain nothing, and for this reason the complete operation for cancer was performed without an exploratory incision. The patient was not under anesthesia, so there was no necessity for hurrying. I conclude from this and other cases that, especially now, when the incidence of cancer of the breast is on the decrease, and benign lesions are on the increase, it is much wiser in all doubtful cases to perform the exploratory excision of the palpable lump and subject it to bisection, naked-eye study and immediate frozen section. And, I repeat, if the lump is still doubtful or border-line, close the wound as if it were benign, and, while waiting for the decision of a number of special pathologists, start irradiation of the axilla with deep roentgen rays. If the growth is typical cancer as agreed upon by the operator and pathologist in the operating room, perform the complete operation at once unless the pathologist recognizes Grade IV acute carcinoma. Then the wound should be closed and deep roentgen ray treatment begun at once and continued.

CASE III.—(Pathol. No. 53438.) (Figs. 3 and 4.) *Provisional Diagnosis.*—Pure comedo or comedo-adenocarcinoma. Clinically doubtful. *Operation.*—Local anesthesia; aspiration biopsy negative. General anesthesia: Complete excision of lump. Nothing found but dilated ducts beneath the nipple. Complete excision of palpable area with nipple. Bisection of specimen after excision: Typical duct cancer or comedo-adenoma in

center. Confirmed by frozen section. On account of the possibility of fully developed cancer, complete operation performed. Glands in axilla, on gross and microscopic examination, negative.

It is important to state here that this case came under my observation May 28, after I had completed my investigation and repeated restudy of this group of breast tumors classified in the Surgical Pathological Laboratory of the Johns Hopkins Hospital by me as comedo-adenocarcinoma. This was about the forty-fifth case. The first was described in 1893, 41 years ago. It was a clinically benign tumor, and all of these tumors have been identical in gross appearance and microscopic histology.

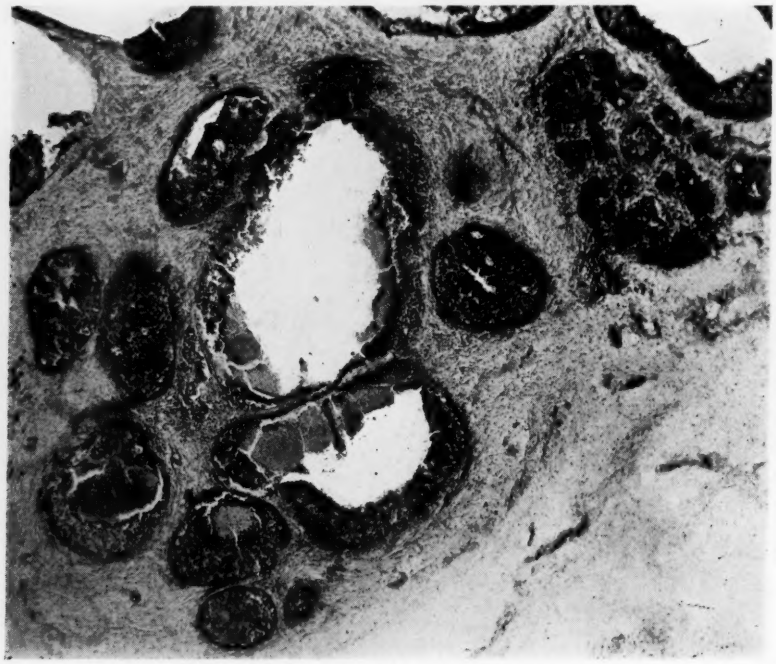

FIG. 4.—(53498.) Typical comedo and atypical breast lobules. Gross shown in Fig. 3. No evidence of malignancy.

I remember the naked-eye and permanent section appearance of the case I helped to explore in 1893 just as clearly as I do the present case. But this last case received preoperative irradiation, and there were much fewer comedos to be expressed. Otherwise the naked-eye appearance was identical with all the others. The microscopic appearance was slightly different. All surgical pathologists know that irradiation may change the appearance of the neoplastic disease, whether benign or malignant. Tumor cells may entirely disappear. Since successful tumor culture of human cancer tissue we know that we may find cancer nests in the irradiated area which appear normal. But these nests will not grow when cultured. Ultimately the determination of the destruction of the human cancer cell may be accomplished in a positive way by cell culture.

In this case of comedo-adenoma without gland involvement, the clinical history and examination placed it in the doubtful group. The palpable area in the upper hemisphere transilluminated distinctly darker than the normal breast or the blue-domed cyst, but not so dark as a solid benign or malignant tumor. There was no fluctuation in the palpable mass. The nipple was slightly fixed and depressed; there had been intensive preoperative irradiation from April 27 to May 2, and my operation was May 31, 29 days later.

CASE REPORT.—She had observed the lump in the upper hemisphere of her left breast one year. The pain had been slight. A month ago there was bloody discharge from the nipple. Irradiation was begun at once, and there has been no discharge of blood since then, but now and then there has been a cloudy discharge, and at our examination we expressed cloudy and serous material from the nipple, of a type not infrequently seen in chronic cystic mastitis. We decided to explore this palpable area.

FIG. 5.—(51020.) Gross specimen bisected, a clinically benign tumor of the breast excised under local anesthesia. Grossly a doubtful tumor without comedo. Microscopic Fig. 6, a pure comedo-adenoma. Immediate post-operative irradiation. Well, July, 1934, almost 14 months. (See Figs. 6 and 7.)

There was nothing distinctly benign or distinctly malignant about it. The history of discharge of blood favored a papillomatous cyst. The duration of the lump of one year favored malignancy. The patient is still menstruating. She is 48. The menstrual periods are changing slightly. There are no other lumps in this or the other breast to suggest chronic cystic mastitis. The lump was sufficiently large to indicate that complete excision would not leave a perfectly symmetrical breast, but the patient begged that the breast be saved even if the symmetry and the nipple were sacrificed.

The patient was prepared for the complete operation. Under local anesthesia there were three negative aspiration biopsies. We could get nothing out of the breast, neither blood, fluid nor cell débris. General anesthesia was then given, and, in view of the history of discharge from the nipple, the nipple zone was included in the area of breast excised. During this excision we passed through normal adenomatous breast. There seemed to be some inflammatory exudate which could be explained by the recent irradiation. When we cut through breast tissue in removing the nipple, we encountered a group of dilated ducts between the nipple and uninvolved breast zone. These ducts

were empty and did not have the characteristic appearance of duct adenoma. The frozen section showed simply dilated ducts, no papilloma, no comedo. I could easily close the defect in the breast and left a but slightly deformed organ. I am confident it would have satisfied the patient, but she had consented to the complete operation, even if I were in doubt. I had no doubt about what I had seen with the naked eye, and in four or five frozen sections, that I was dealing with a pure and relatively benign type of comedo-adenoma. But I had not seen under the microscope *all* the areas, and the area was too large to make frozen sections from every part. Before 1915, in a somewhat similar case, I rested my diagnosis on the naked-eye appearance and found later, in the laboratory, areas of fully developed cancer, and then I performed the complete operation and found the glands to be involved. For this reason, in this case, I decided to perform the complete operation, which was done by my associate, Doctor Cohn. The glands were negative. I wish to repeat, I think this was the safest thing to do. But this comedo-adenoma is a rare tumor. When the tumor is of one month's duration, it is smaller than a 25 cent piece, and the entire tumor can quickly be studied in the frozen sections. I have one such case now. (Figs. 5, 6 and 7.) It is more than two years since the excision of the tumor and immediate postoperative irradiation. The wound broke down and healed by granulation. The patient is well today without palpable glands in the axilla. I might state here briefly that comedo-adenocarcinoma in its pure state does not metastasize to glands. None of these patients has died of cancer. One of them lived over 35 years. All of them lived over five years.

The tumors have varied in size from a ten cent piece to involvement of the entire breast. The breast may ulcerate and produce a fungous tumor. They may be clinically benign or clinically malignant, they may grow rapidly or slowly. They are all identical in gross and microscopic appearances. They may be mixed with fully developed cancer of the medullary type, and in many of these cases the only way to make a distinction is with the microscope. The definite presence of comedos in the cut surface of a breast tumor or in the frozen section does not exclude the presence of malignant areas. In the very small tumors typical gross comedos may be absent. Ultimately I think we shall be able to distinguish them in small tumors of the size of a 25 cent piece or less and confine our operation to the removal of the tumor only. We ultimately may even give up postoperative irradiation.

Conclusions.—In those clinics in which the great majority of the patients have observed their breast condition one month or less, in fully 85 per cent of the cases any operative procedure, except an aspiration biopsy, will be excluded by the most careful palpation and transillumination. There is no objection to taking roentgen ray films of the breast. In my experience this cannot compete with transillumination. In these clinics in which only 15 per cent of the patients are placed on the operating table and prepared for the complete operation, the majority of the tumors will be clinically benign and the method of biopsy by excision of the lump as practiced in two of the cases reported here will be employed. This method of biopsy will be employed in some cases clinically malignant, yet doubtful. I see no objection to an aspiration biopsy first, but I would not allow a negative aspiration biopsy to influence anyone in the exploration by excision and examination of the lump by the naked eye and frozen sections. Judging from the tissues sent to me and to the Surgical Pathological Laboratory of the Johns Hopkins Hospital for

examination, surgeons and their pathologists are encountering more difficulties in distinguishing these early breast tumors. The method of biopsy is by excision of the tumor. The surgeon is in doubt as to its gross appearance and the pathologist as to the frozen section. The tumors received are rarely blue-domed cysts or encapsulated adenomas. They are non-encapsulated areas in the breast. The great majority are distinctly benign border-line tumors. A few are malignant.

These border-line tumors are being cut into sections and are submitted three times each year to an increasing number of surgeons, pathologists and radiologists interested in breast lesions, and there is always disagreement, with the majority in favor of benignancy. These border-line breast tumors have all been followed up. In the greater number the breasts have not been removed. None so far has developed any sign of cancer.

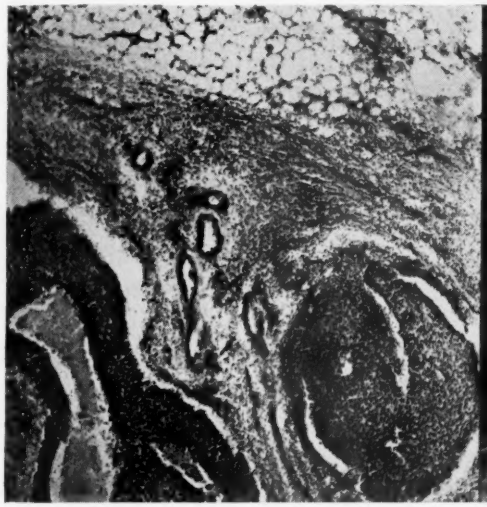

FIG. 6.—(51020.) Immediate frozen section of benign tumor of breast shown in Fig. 5. Pure comedo-adenoma in capsule of tumor, breast parenchyma. Beyond this fat. Patient aged 44. Tumor of three weeks' duration.

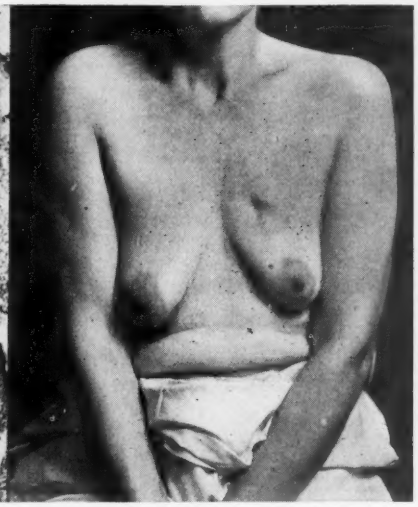

FIG. 7.—(51020.) Photograph of patient about ten months after operation. No recurrence. No involvement of the axilla. Clinically well.

There are two cases in which the pathologists differ evenly as to the final diagnosis. In one it is more than three years since the exploratory biopsy, in the other more than two years. One of these cases is a lactating adenoma, the other tumor is a comedo-adenoma, and the difference of opinion is whether it contains areas of fully developed cancer. In this latter case, the comedo-adenoma, the disease was not completely removed, as it involved so much of the breast. There was no pre- nor postoperative irradiation. I have felt this breast within a month, almost three and one-half years after the exploratory biopsy by my associate, Doctor Cohn. There is no recurrence. Concerning these border-line tumors there is a distinct difference of opinion between my associates who are both surgeons and surgical pathologists and between the surgical pathologist in the laboratory.

Until we get a differential stain or until we take up the training of pathologists in the operating rooms of this country, more and more breast tumors as well as other tissues from the operating rooms will have to be submitted to two or more diagnostic clinics during which time the patient may receive irradiation. This is going on now in a very satisfactory manner. There is beginning to be a feeling of responsibility by the larger medical schools and clinics, and they offer more opportunities to young men and women for special study of benign and malignant tumor tissue, as well as in the technic and use of the deep roentgen rays and radium for irradiation. There should be as much opportunity given for the study of tissue diagnosis and irradiation methods as to operative procedures. There is a greater demand today for pathologists and radiotherapeutists than for operators.

The evidence that I have up to date indicates that when a surgeon removes a tumor of the breast and he and his pathologist or he without his pathologist, are doubtful as to the diagnosis, there is no added risk (providing the tumor has been excised by cutting through normal breast tissue, the wound has been closed, the axilla irradiated at once, the breast and the wound irradiated in five to ten days) while waiting, if sections of this doubtful border-line tumor are submitted to a number of the best microscopic diagnosticians. Then if they get the unanimous opinion of malignancy they can perform the complete operation. This statement is absolutely the reverse of what I have advocated in previous publications, but it is forced upon me by facts just as the previous statements were. The breast tumor of one month's duration, even when microscopically malignant, is a different tumor from that present six or more months, and there seems to be additional evidence that pre-operative irradiation, when the tumor is clinically malignant, and after the excision of the small lump for biopsy, offers a better chance of a permanent cure than a complete operation without preoperative irradiation.

The old rule of "When in doubt, perform the complete operation for cancer of the breast" following the rule of Halsted, no longer holds good. Nor should the complete Halsted operation be performed when the breast tumor is clinically malignant. When the breast tumor is clinically malignant, and when the biopsy is doubtful, preoperative irradiation should be the rule.

There is a great difference of opinion among experienced surgeons, pathologists, radiologists and radiotherapeutists on many questions in regard to biopsy and when irradiation should be given, how it should be administered, and how long one should wait before operating after preoperative irradiation. The evidence at hand seems to confirm the following statements: There is no reason for hurrying irradiation. One may take at least three months and then perform the complete operation for cancer. Just how much time one should take for irradiation no one knows yet, but apparently three months is sufficient for at least two thorough courses of the Coutard or some other type of roentgen ray irradiation, with and without the implantation of radon seeds. An agreement on this period of time in which we are justified by the evidence

to wait between the administration of irradiation and the biopsy or the complete operation for cancer, has not yet been reached.

The next point about which there is also much disagreement is, what to do when the microscopic study of the clinically benign or doubtful tumor of the breast leaves the pathologist and surgeon still in doubt. If the pathologist is an experienced one and he has no doubt that the breast tumor is malignant from the microscopic picture, there is no objection to proceeding with the complete operation for cancer. It is possible that perhaps the patient's chances of a permanent cure are better when irradiation precedes the complete operation. If this proves true, then, when the biopsy on the operating table on a patient prepared for the complete operation shows definite malignancy, even in such an instance one should close the breast wound and begin irradiation, deferring the complete operation for three months.

When the glands in the axilla are not involved, the five year cures are about 70 per cent. When the axillary glands are involved the five year cures drop to 25, 20 and 10 per cent according to whether the base, mid or apical glands are involved. These results when the glands are involved depend largely on the skill of the operator. Apparently postoperative irradiation has not influenced five year cures. We have not had enough experience to know what preoperative irradiation will accomplish. However we feel quite certain that if women seek a proper examination within one month, the incidence of cancer will be less than 10 per cent. Between six months and one year it reaches almost 80 per cent. The majority of palpable tumors of the breast of less than one month's duration will be some type of chronic cystic mastitis, and when we exclude from this number those in which we can recognize benignancy without biopsy, by palpation and transillumination, there will remain about 15 per cent of tumors that must be explored, and when these are correctly diagnosed microscopically, much more than one-half of them will be found to be noncancerous.

The type of surgery for the benign and for the malignant tumor in the breast is settled, but when the operation should be performed is not settled. At the present time, if proper postbiopsy irradiation is given, there is no danger from the delay of the complete operation, during which time sections or pieces of tissue from the mass excised may be submitted to two or more pathologists for diagnosis.

CLASSIFICATION OF MAMMARY CANCER

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A SATISFACTORY classification of mammary cancer would be of great value as an aid in diagnosis, prognosis and treatment, it would facilitate discussion and the spread of knowledge, and by providing a uniform nomencla-

ture it would permit the gathering of comparable statistics on the results of treatment.

Such a classification must be based on pathologic anatomy, histogenesis, and structure, which determine the gross appearance and course of the disease, but it must fit the clinical aspects of the disease which impress the surgeon who has to deal with the patient. It would seem that present knowledge is sufficient to permit the adoption of some scheme which would cover all but the very rare varieties of cases. We submit the following plan for consideration.

(1) *Adenocarcinoma Arising in Cysts.*—This is the most characteristic type of mammary cancer. It arises in cysts, in the walls or in papillary growths within cysts, or it arises from an isolated segment of breast tissue. The architecture of the blood system in these tumors is dendritic, so that they grow expansively, displacing rather than infiltrating the breast tissue, and tending to produce a single multilobed compact mass. In any case, the growth is encapsulated or circumscribed, and infiltration occurs only in the later stages.

These tumors will grow to large dimensions, often rapidly. They protrude and often fungate through the skin, with ulceration, bleeding, and sloughing. The invasion of lymph nodes is delayed, but only in accordance with the grade of malignancy. Many of them long spare the nodes, so that the prognosis is generally better than the extent of the local disease suggests.

(2) *Mucous or Gelatinous Carcinoma.*—This is an adenocarcinoma with mucous degeneration of stroma and fat tissue. The mucous change often retards the growth of the tumor cells, so that the total duration is distinctly longer than that of other adenocarcinomas. It presents the same gross appearance as ordinary adenocarcinoma, but the mucus gives bulk and elasticity to the tumor, and when it is very abundant, the tumor cells may largely disappear and the tumor areas are largely represented by mucous cysts.

(3) *Duct Carcinoma.*—This variety occurs in two main forms. (*a*) Localized duct carcinoma, and (*b*) diffuse duct carcinoma.

(*a*) Localized duct carcinoma. Comedo-carcinoma. This condition occurs in small breasts without much fat tissue, in which a segment of ducts, often about the nipple, or in any segment, becomes slowly distended with inspissated secretion which exudes from the cut section as yellowish or dark material. The breast is usually reduced in size, but a hard palpable tumor is present, and the nipple is early retracted.

(*b*) Diffuse duct carcinoma. This condition arises in large fat breasts in which the ducts are held apart by the fat tissue. It begins in a segment of a duct, and extends along the duct system, even involving the entire breast, which becomes enlarged, swollen, edematous, with pigskin appearance, but a definite localized tumor is missing.

Small infiltrating and metastasizing duct cancers may arise in any portion of the breast, and when highly malignant they are responsible for most of the unexpectedly bad results of radical operation.

There are all grades of malignancy in duct cancers, but infiltration of breast tissue and extension to lymph nodes are relatively early.

It is well known that the majority of breast cancers arise from duct epithelium, but in the cases here classified, the relation of the process to the ducts and its extension along the ducts is so prominent as to yield peculiar anatomic and clinical features. It is not impossible that peculiar etiologic factors are also involved.

(4) *Paget's Disease.*—This is essentially a duct cancer, which begins in a segment of one or more large ducts, usually in or beneath the nipple, and extends outward over the nipple and areola, or downward to the deeper portions, and often in both directions. It may be found exclusively in nipple and skin, or only in the ampulla, or only in the large terminal ducts. It may grow slowly and long fail to infiltrate the breast tissue, but it may spread along the ducts and prove as malignant as any form of mammary cancer. A definite tumor is often missing.

(5) *Carcinoma Arising on Chronic Mastitis.*—A definite grade of chronic mastitis occurs in a considerable proportion of breasts which are the seat of carcinoma. Usually the remaining breast shows simple atrophy, with or without fat hypertrophy. Hence, comes the rule that a single very hard nodule in an otherwise normal breast is nearly always cancer.

In the present group of cases the changes of chronic mastitis are prominent, and the carcinoma appears to be the sequel of the mastitis. The mastitis may take the form of any one of the three main varieties, cystic, nodular, or diffuse. One or more of the cysts, nodules, or thickened ducts becomes enlarged, very hard, more or less fixed, or adherent to skin, and presents the usual features of infiltrating carcinoma. Multiple foci of carcinoma are not uncommon. A common condition is a tight nipple, thickening of the large ducts, then a zone of cysts or hard nodules, and on the outskirts of the breast a single very hard nodule of definite carcinoma.

The histologic types and grades of malignancy in carcinoma arising on chronic mastitis vary widely. Ducts, acini, sweat glands, the walls of small cysts, papillary adenocarcinomas growing into cysts, all contribute a quota. The histologic structure is often mixed and confusing. As a rule, the grades of malignancy average lower than in most other varieties, but the disease is often fully malignant and dangerous.

(6) *Sweat Gland Cancer.*—Many of the more cellular and malignant carcinomas arising from sweat glands are difficult to distinguish histologically from duct cancers, and the clinical features are not peculiar, but when the cancer arises from the glands on the outskirts of the breast, or when the tumors are of moderate malignancy, they constitute an easily recognizable clinical variety. These tumors arise in or just beneath the skin, on the edges of the breast, along the mammary fold, and slowly protrude and ulcerate through the skin. They are firm but not fibrous, smooth, yellow, and generally dry and free from necrosis and edema. Cellular tumors of sweat glands produce any of the common anatomic or clinical varieties, except Paget's disease. They are often mucous.

(7) *Inflammatory Carcinoma.*—This is clinical variety, characterized by rapid growth, diffuse spread over wide areas of skin, with erysipelatous reddening, heat, and edema. It usually arises on a basis of a preexisting diffuse infiltrating duct carcinoma. It is sometimes associated with some secondary infection, but its exact causation is unknown. The reddening of the skin is due to diffuse infiltration of the dermal lymphatics or blood vessels, by rapidly growing tumor cells, accompanied by edema and lymphocytic infiltration.

Many cases of carcinoma of the breast show some signs of inflammation of the skin, but the tendency to identify many such milder cases with true inflammatory carcinoma is to be avoided.

(8) *Histologic Designations.*—The chief source of confusion in the nomenclature of mammary cancer is the tendency to employ histologic terms instead of well defined anatomic and clinical types.

Medullary carcinoma refers to any very cellular tumor, usually an adenocarcinoma.

Scirrhus carcinoma is a clinical term for advanced fibrocarcinoma involving much of the breast with atrophy.

Fibrocarcinoma refers to any highly fibrous structure, which may arise in almost any type of tumor.

Cancer *en cuirasse* refers to the encasement of the chest wall in cancer tissue, usually of fibrous type.

Carcinoma simplex designates the usual structure of fully developed infiltrating carcinoma.

None of these terms should be employed as the primary entry for any clinical or anatomic variety of mammary carcinoma.

SURGICAL PRINCIPLES IN CANCER OF THE BREAST

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THE operative treatment of carcinoma of the breast dates back almost to the beginning of medicine. Astley Cooper in the early part of the last century recognized the importance of the involvement of the axillary nodes and removed some, but at that time no radical operation was attempted, although I believe that the desirability of the radical removal of the nodes is indicated in the article which he published.

Lister deliberately planned and performed a radical operation and, as far as I know, this is the first instance in which a radical removal and block dissection of the axillary nodes was carried out. Some years later Heidenhain, Willy Meyer and Halsted devised operations in which a block dissection of the axillary contents and a radical removal of the breast was attempted. While the technic varied considerably, the ultimate object was the same. In

one operation the dissection was carried from below upward, the axillary dissection being done last; while in the other operation the axillary dissection was performed first, as the bleeding is much better controlled when the vessels are ligated first. They are no longer encountered repeatedly as when the dissection is carried from below upward.

Since these operations were devised, there has been at times a tendency to perform a less radical operation. There has been a great deal of discussion as to whether the pectoral muscles should be sacrificed, or as to whether it is not the best procedure to remove the pectoralis major and leave the minor. Bryant of London said some years ago that he had not seen a recurrence of carcinoma in the pectoralis major, and that, if the fascia covering the pectoralis major were removed, the necessary precaution to prevent recurrence in the muscle had been taken. Recurrences have been observed in the pectoralis major. The function of the arm is not interfered with when both muscles are removed, and a satisfactory axillary dissection cannot be made unless they are removed. In some of the discussions which have been carried on Groszman's lymphatic path seems to have been forgotten. The lymphatics described by Groszman pierce the pectoralis major muscle and empty into lymph nodes described by Rotter which are found in the upper part of the axilla. These cannot be satisfactorily removed unless the axilla is carefully exposed after both muscles have been divided. As there is no alteration in the motions or interference with the same, there is no reason why these muscles should not be removed.

In the operation, in order to prevent limitation of motion, an axillary skin flap should always be made, which can be tucked into the axilla and so applied that the motions of the upper extremity will be perfectly free.

Too much rather than too little skin should be removed, and not infrequently skin grafting will have to be resorted to. Removal of skin prevents recurrences in the form of lenticular carcinoma.

Surgical elephantiasis remains one of the distressing sequelae. I think that I have seen it most frequently after incomplete operations, especially in those cases in which the apex of the axilla has not been dissected. It occurs also in those cases in which serum has been allowed to accumulate and after infections. A clean dissection with a sharp knife, without tissue damage, is the best safeguard against this sequela. In some cases no explanation can be given, and in such instances there may be anomalous distribution of the lymphatics.

There is a tendency to limit the degree of radicality, and I do not believe that as radical and good operations are done, as a rule, as when this radical procedure was first undertaken.

A radical operation should be performed, and no degree of radicality, based upon the size of the tumor, practised. An operation should be resorted to in all cases, except when there is no hope of effecting a cure. Some cases which I have operated upon with little hope have survived long periods.

THE VALUE OF PREOPERATIVE IRRADIATION IN BREAST CANCER

STUDIES ON EIGHTY-ONE OPERABLE CASES

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IT HAS been most difficult to evaluate the statements made by various authors on the value of preoperative irradiation in cases of breast cancer. Some authors, especially radiologists, have enthusiastically and unqualifiedly stated preoperative irradiation to be of great value without giving their criteria for such conclusions. On the other hand, some surgeons have been completely unwilling to accept the considered thought of cautious students of irradiation. The truth must lie somewhere between these points of view.

In an effort to evaluate preoperative irradiation we have taken 81 patients having operable mammary cancer and subjected them to preoperative irradiation. Part of them were treated (39 cases) by the radium element pack; while 42 cases were treated by the high voltage (200 K.V.) roentgen rays. Approximately a two to three months' period followed the completion of the irradiation, when a radical amputation was performed. Careful tissue studies were then made of the residual tumor. Certain deductions have been drawn as to the efficacy of the type of the irradiation applied, and also as to the amount supplied.

In each case here reported a positive aspiration biopsy complemented our clinical diagnosis. There are some who may feel that aspiration biopsy is not a certain method of biopsy; however in the Memorial Hospital it has come to be fully relied upon. Unless we have a report of a positive cancer by this method, we have excluded that case from these studies.

Radium Element Pack Cases.—Thirty-nine cases were subjected to treatment using the radium pack (4 Gm.) at a distance of 6 cm. Five ports were used, namely: (1) The breast mesially; (2) the breast laterally; (3) the axilla anteriorly; (4) the axilla direct, and (5) the axilla posteriorly. By this method, the tumor in the breast was cross-fired in two directions while the axilla was cross-fired in three directions. Fifteen cases were subject to treatment using 20,000 M.C.H. per port; two cases, to 22,000 M.C.H. per port; 20 cases, to 24,000 M.C.H. per port; one case, to 28,000 M.C.H. per port, and one case, to 44,000 M.C.H. per port. In some instances as a result of such intense irradiation at such a short distance, the skin denudation persisted, becoming a chronic nonhealing ulcer. In these cases the operation did not take place before a three or four months' period after irradiation ceased. The radical Halstead operation was then performed, removing the muscles and all axillary contents. Careful studies were then made and revealed that there had been a most striking effect on the original tumor in a

large part of the cases. Of the 39 cases so treated it was found that eleven, or 28 per cent, of the tumors had completely disappeared, so that no trace of cancer tissue remained in the breast after the most careful studies had been made.

Scale of Irradiation Effect.—These studies have led us to the conclusion that a scale of irradiation effects would be of great value; the following was therefore devised:

R.E. 0: Signifies that irradiation destruction is most incomplete and has been minimal. It may signify that there was complete destruction in one area with persistence of viable disease in another area.

R.E. 1: Signifies that we have the minimal effects of irradiation such as atrophy, hydrops and slight sclerosis.

R.E. 2: Signifies a more marked condition but a similar one.

R.E. 3: Signifies that the process of irradiation destruction has been extremely marked, and that there is a question whether the tumor cells are viable or not. It will remain for the element of time to prove whether this R.E. 3 group is capable of regeneration or metastasis. Doctor Ewing is of the impression that the cases falling into this group may eventually be completely cured and incapable of recurrence. We are taking the position, at least for the present, that this group may be capable of recurrence.

R.E. 4: Signifies that after a most careful study has been made of tissue taken from many portions of the breast, there is no sign of any demonstrable cancer.

Following out this same idea as above applied to the breast, we have made similar studies on the axillary nodes. Their irradiation classification scale would be N. 0; N. 1; N. 2; N. 3; N. 4. The clinical studies of these cases, although they parallel the microscopic studies in many instances, are not as a rule a reliable criterion. The following is a table showing the clinical changes which took place in the breast and in the axillary nodes.

TABLE I

RADIUM ELEMENT PACK

	Breast		Nodes	
	Cases	Percentage	Cases	Percentage
Complete clinical disappearance	15	40	6	33
Only residual thickening	11	30	–	..
Marked reduction	9	23	8	44
No change	3	7	4	22

The following table gives the scale of irradiation effect according to the above described criteria:

TABLE II

Radiation Effect (R.E.)	0	1	2	3	4	
Cases	11	7	3	7	11	BREAST
Percentage	28	18	8	18	28	
Cases	11	1	.	1	2	NODES
Percentage	73	6.5	.	6.5	13	

If it were possible to add R.E. 4 and R.E. 3 there would be 46 per cent of the cancers in the breast which received these profound changes. Similarly, in the case of the nodes, if we could add N. 4 and N. 3, there would be 19.5 per cent, which is one in five cases.

It is perfectly obvious that we are failing to cure axillary nodes in a very high proportion of the cases. It is also obvious that we are curing cancer situated in the breast itself in better than one out of four cases by such an external irradiation method as this. On account of these facts, we have devised a new method of radiating the axilla by the placing of a radium string across it which we hope, after sufficient experimental work has been done, will accomplish a much greater sterilization than has heretofore been possible.

New Method of Radium String.—A rubber catheter is employed. Into this catheter are inserted in tandem form, six silver tubes, containing radium emanation each 16 Mm. long. These capsules are separated from each other by a cord knot so that there is a space between each of the six capsules of about 3 Mm. each. The filter of the capsule is equivalent to one millimeter of platinum. The length of the radium bearing area is about 11 cm.

Under local anesthesia a long uterine dressing forceps with a slight curve at the end of the blade is pushed through the axillary fascia, parallel to the axillary vein going behind the pectoralis major muscle and the pectoralis minor muscle. The point of the clamp is then brought up through the pectoralis major muscle and on through the integument at the edge of the sternoclavicular joint (Fig. 1). This can easily be accomplished by holding the arm out at right angles to the body. Novocain is used only at the site of entrance through the skin of the axilla, and also at the site of emergence at the sternoclavicular joint. The point of the dressing forceps, while still *in situ*, then grasps the free end of the catheter, which is then pulled backwards through the tract by the forceps. The radium string is held accurately in place by one suture. It is not necessary to make more than a 1 cm. skin incision at either end. If one proceeds carefully and slowly with the point of his clamp turned caudally, he will not run the risk of tearing a hole in the subclavian vein. One must also advance the point of the clamp carefully in order to avoid the possibility of tearing one of the smaller veins which cross the axilla emanating from the subclavian and axillary veins. We have employed this method of axillary irradiation in 30 cases. In no instance have we encountered any difficulty with the axillary vein or its branches while placing the radium string (Fig. 2). We, therefore, do not hesitate to recommend this procedure. Naturally we started most cautiously in these studies for fear of obtaining a brachial neuritis on account of the proximity of the brachial plexus to the axillary string. In these 30 cases we frequently consulted our physicist, Doctor Quimby. We began by using three S.E.D. 3 Mm. from the source of the radium. This amount has been gradually increased to seven S.E.D., and during this time, no case has shown neuritic symptoms. It may be possible to run this amount of irradiation up to where we are

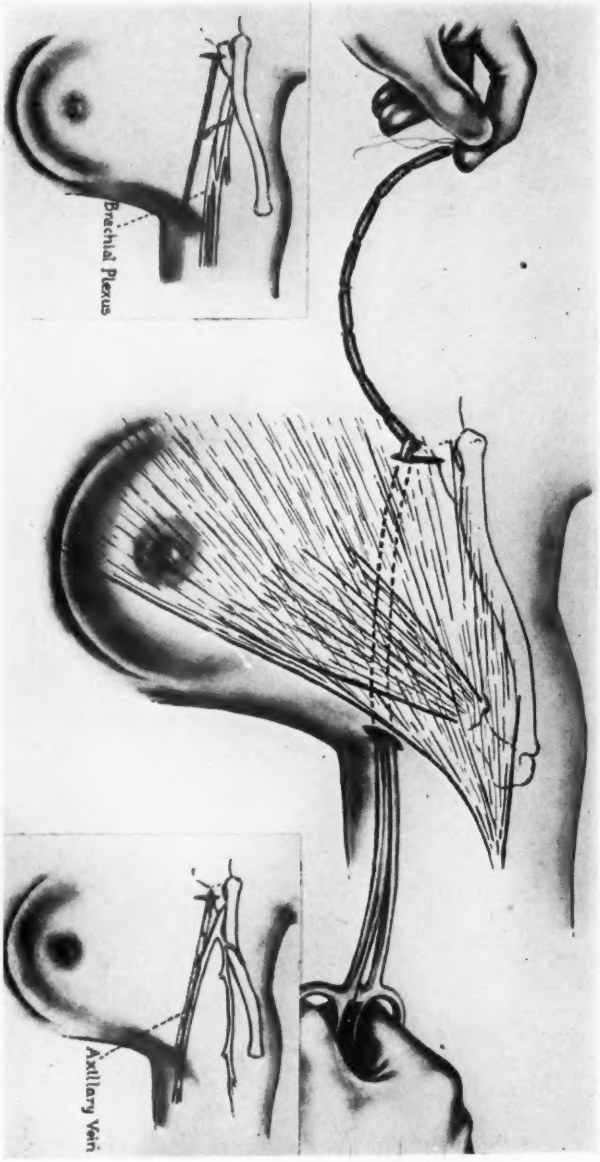

FIG. 1.—Showing the uterine dressing forceps behind the pectoralis major and pectoralis minor muscles. The tip protrudes through the skin near the sternoclavicular joint. It grasps the end of the rubber catheter which contains the six radium capsules. The forceps are then withdrawn leaving the radium string in situ.
One insert shows the radium string in relation to the brachial plexus. The other insert shows the relation of the radium string to the axillary vein.

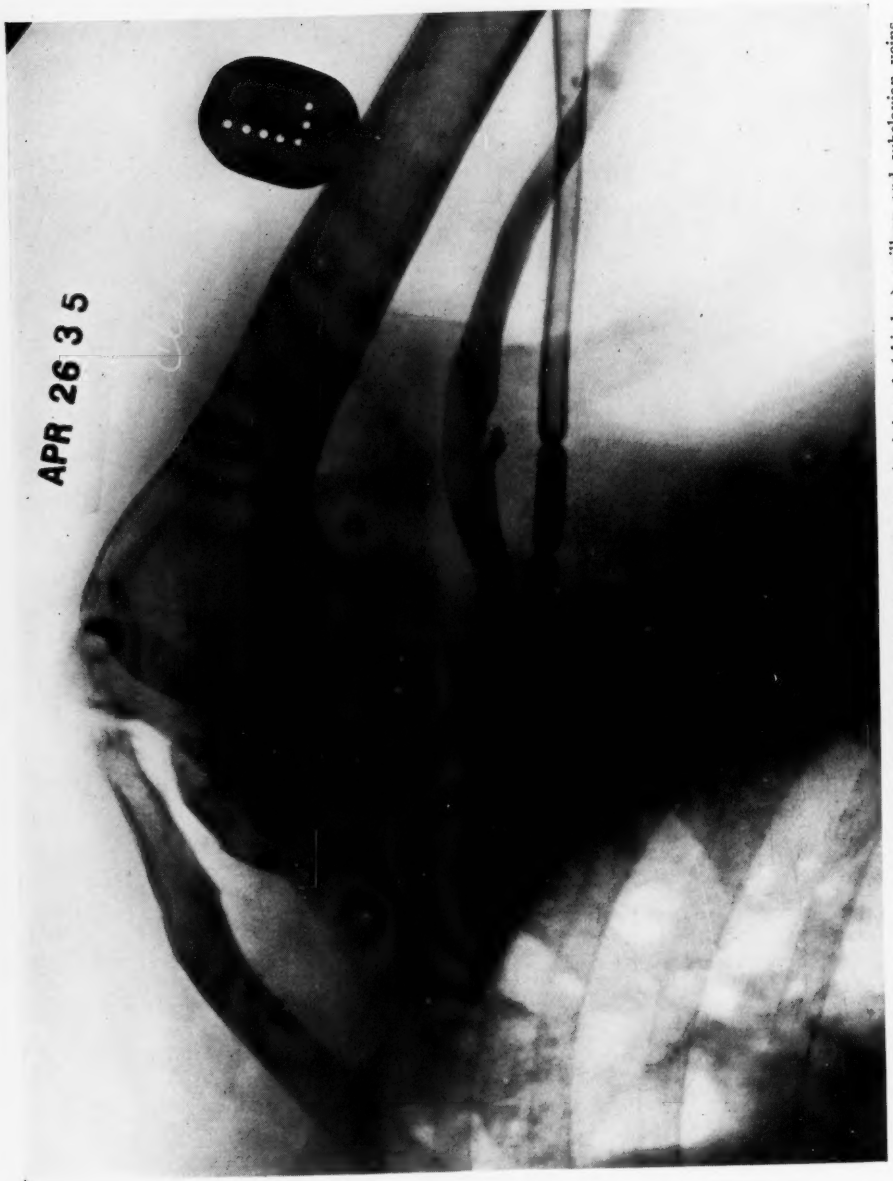

FIG. 2.—Showing the relative position of the radium string in relation to the injected (skiadan) axillary and subclavian veins in the living subject.

obtaining a cylinder of sterilization which may be three to five cm. in diameter. If this becomes possible, without the production of neuritis, this method will be a distinct advance in radium therapy.

These cases are being reported from the standpoint of experimental studies. It remains to be seem what will be the effect five years hence on increased cures over our present surgical results, namely 35 per cent, where preoperative irradiation is not employed.

In the study of these cases treated by the radium pack, it was found that where 20,000 M.C.H. was employed per port, that we had no case of a persistent ulcer of the skin. However, when we went up to 24,000 M.C.H. per port, we found that of the 20 cases so treated, 12 or 60 per cent had a persistent ulcer of the breast. Furthermore, we found where the cases were treated by 24,000 M.C.H. per port, that our largest group of completely destroyed tumors occurred. This was likewise true in the successful destruction of the nodes. One of the disadvantages of treating the mammary gland by these higher doses of radium is the complication which ulceration makes at the time of operation. If the breast is infected, it is very easy to obtain lymphedema of the arm. In most of the cases where there had been a R.E. 3, and R.E. 4 effect, it was impossible to grade the cancer on the scale of malignancy, as destruction had proceeded too far.

The size of the tumor appears to play a rôle. It seems from a study of the lesions that a tumor having a diameter of 2 or 3 cm. has a much better opportunity of complete regression than one of great bulk. In the latter case it frequently happens that the large part of the tumor is completely necrotic but the very periphery may be viable. We have taken arbitrarily from two to four months after the completion of irradiation as the time chosen to do the radical amputation. This was chosen partly on account of the fact that most irradiation effects are accomplished during this period. In the cases treated by the high voltage roentgen ray, the skin, although markedly damaged, usually cleared up within two to three weeks after the completion of treatment. The radium pack produces a slower skin damage than the high voltage roentgen ray. One disadvantage of the radium element pack is that the ports are not of sufficient size, so that in a large woman with pendulous breasts, it is not an instrument which as completely covers the breast and its drainage areas as does the roentgen ray. We believe that one of the main advantages of the radium pack is its effectiveness in superficial tumors. The axilla is such a large space that the roentgen ray may prove to be a better agent for treatment.

200 K.V. Roentgen Rays.—Forty-two operable cases were treated by the 200 K.V. roentgen ray machine. To some we gave 1,200 *r.* to each of six ports; in some cases, 1,500 *r.* per port were given, and in a few, 1,800 *r.* per port. Three hundred *r.* were delivered to each of three ports daily until the required amount was given. One-half Mm. of copper filter was used. This dose was somewhat lighter in most instances than the doses delivered by the radium pack. However, even though the doses were lighter, there

were seven out of 42 cases that had complete microscopic disappearance of the tumor.

The following table shows the clinical changes taking place in the breast and in the axillary nodes:

TABLE III

200 K.V. ROENTGEN RAYS

	Breast		Nodes	
	Cases	Percentage	Cases	Percentage
Complete clinical disappearance	13	34	8	28.5
Only residual thickening	4	11	..	....
Marked reduction	8	21	8	28.5
No change	13	34	12	42.5

The following table gives the actual scale of irradiation effect:

TABLE IV

200 K.V. ROENTGEN RAYS

Radiation Effect (R.E.)	0	1	2	3	4	
Cases	18	5	4	8	7	BREAST
Percentage	43	12	10	20	16.5	
Cases	16	6	1	2	0	NODES
Percentage	64	24	4	8	..	

CONCLUSIONS

It is shown that the radium element pack as applied in a group of 39 cases destroyed the breast cancer in 28 per cent of the cases. In a similar group of 42 operable cases treated by the 200 K.V. roentgen ray machine the breast cancer was destroyed in 16.5 per cent. It is also shown that external irradiation as applied in this series did not effectively combat axillary disease; and this fact points to the necessity of giving additional interstitial irradiation. A method is above described which will unquestionably improve our results. A new scale of irradiation effects is described; it has been of assistance to us in these studies. It is our impression that eventually irradiation will be given in smaller doses, and extended over a longer period of time; and that end-results will be improved thereby.

In the light of the studies here reported it is our impression that the five-year cures will be definitely increased by the employment of preoperative irradiation; and that it should be employed in all instances of cancer of the breast complicated by pregnancy; in cases with bulky axillary disease; and in those of cancer in young women.

NOTE. We are indebted to Doctor Duffy for seeing that the problem was carried out as outlined in the Radium Pack Department. We are likewise indebted to Doctor Herendeen for similarly carrying out the details of the problem in those cases treated by roentgen rays; and to Doctor Quimby, we are deeply obligated for encouraging us and guiding us in the details of the physicists' problems.

BONE GROWTH AND REPAIR*

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GROWTH and repair are properties of living matter that have a great deal in common, and a study of one may yield results of importance in the understanding of the other. In certain lower forms of animal life and in the least specialized tissues of higher forms, repair may be almost identical with growth except in the matters of time, velocity and the nature of the stimulus bringing it about. Thus, repair following amputation of the leg of a salamander or the tail of a tadpole may proceed to the point of complete restitution of the missing part with its various types of tissue, and repair following injury of certain epithelial and connective tissues in man may approach the same order of perfection. Bone is one of the tissues in which repair simulates growth both in its physiologic and morphologic processes to a very considerable degree.

Bone growth takes place by two types of ossification: ossification through cartilage and ossification through fibrous tissue or membrane. The bones of the vault of the skull, parts of all the facial bones and the clavicles are performed in membrane and grow by fibrous ossification. The reason for this is to be found in comparative anatomy and paleontology. The earliest vertebrates or selachii which included the sharks had a cartilaginous skeleton. The head had cartilaginous jaws and base of the skull, but the vault of the skull was composed of membrane. In the succeeding phylum which included the bony fishes a layer of dermal bone or exoskeleton appeared over vault of skull, jaws, throat and gill regions. The prevailing theory, according to Romer,[1] is that this developed as a defense mechanism against the deadly attacks of their eurypterid or crab-like enemies. This dermal bone disappeared in places in early land animals and all that is left in man is in the vault of skull, face bones and clavicles, which structures have gradually sunk beneath the skin and articulated with the endoskeleton. They are a lasting memento of the successful struggles of our earliest vertebrate ancestors against enemies that became extinct hundreds of millions of years ago.

The rest of the bones, while preformed in cartilage, grow partly by enchondral ossification and partly by fibrous ossification. Increase in length of shafts through the epiphysial lines and in size of the bony centers of the epiphyses is by enchondral ossification, while transverse growth of shafts and transformative growth of cancellous bone in the metaphyses and epiphyses is by fibrous ossification. As growth continues the enchondrally formed bone, which is increasingly farther separated from the epiphysial line, is gradually replaced by bone formed directly by fibrous ossification. When maturity is

* The Arthur Dean Bevan Lecture of the Chicago Surgical Society, 1934.

reached all that remains of the enchondrally formed bone is the major portions of the epiphyses and metaphyses.

Each pair of long bones differs in the relative amounts of longitudinal growth taking place at the two ends. These amounts have been variously determined as by measurements after arrest of longitudinal growth either experimental or accidental, after implantation of metallic markers, after the administration experimentally of madder or elizarin red to discolor the newly formed bone and after the formation of dense transverse metaphysial bands or lines of bone during periods of phosphorus therapy, or after severe illnesses, as scarlet fever. Digby[2] prolonged the axis of the nutrient artery of adult bones to the center of the marrow cavity, at which point ossification presumably began and measured the distance from there to either end of the shaft. His amounts of growth at the two ends of the shafts were as follows: Femur, u.e. 5 in., l.e. 11 in. Tibia, u.e. 7½ in., l.e. 5 in. Fibula, u.e. 7½ in., l.e. 5 in. Humerus, u.e. 9½ in., l.e. 2½ in. Radius, u.e. 2 in., l.e. 6 in. Ulna, u.e. 1¾ in., l.e. 5⅝ in.

Measurements in 25 children from transverse lines or bands produced by phosphorus medication or by illnesses have been made by Dr. C. Howard Hatcher in the University of Chicago Clinics, which, in percentages of growth gave the following results: Femur, u.e. 21 per cent, l.e. 79 per cent. (Fig. 1). Tibia, u.e. 56 per cent, l.e. 44 per cent. Fibula, lines are often indistinct before appreciable growth increment, but when distinct the percentages approximate those for tibia. Humerus, u.e. 84 per cent, l.e. 16 per cent. Radius, u.e. 18 per cent, l.e. 82 per cent. Ulna, uncertain because of early fading of lines, but similar to radius. These figures approximate those obtained by Digby for humerus and femur but show a greater difference for radius and more nearly equal growth for tibia. Operative arrest of longitudinal growth by excision of the epiphysial cartilage line and sliding bone grafts on either side has been used in selected cases to retard growth in the longer limb, in case of shortening from disease or injury and thus equalize limb length (Phemister[3]). This necessitates a knowledge of the amount of growth at each epiphysial line in order to determine the appropriate age for operation and the number of epiphysial lines to be fused. Experience has shown that estimations may be made that are of sufficient accuracy to yield satisfactory results.

The age of completion of longitudinal growth for each bone varies directly with its size and with the relative amount of growth from either end. In general the shorter bones stop increasing in length first, as does that end of a bone from which the lesser increment occurs. The greatest difference between ends is seen in the humerus. At the lower end where 15 to 20 per cent of the increment takes place, growth stops at 13 to 15 years, whereas at the upper end where the other 80–85 per cent takes place, it stops at 18 to 20 years. The bones of females reach their full longitudinal growth on an average of two years earlier than males. The velocity of growth varies considerably with

age and with the date of establishment of puberty. There is a growth spurt during approximately the two years preceding puberty which, according to Baldwin and Todd, is somewhat less marked in the bones of the extremities

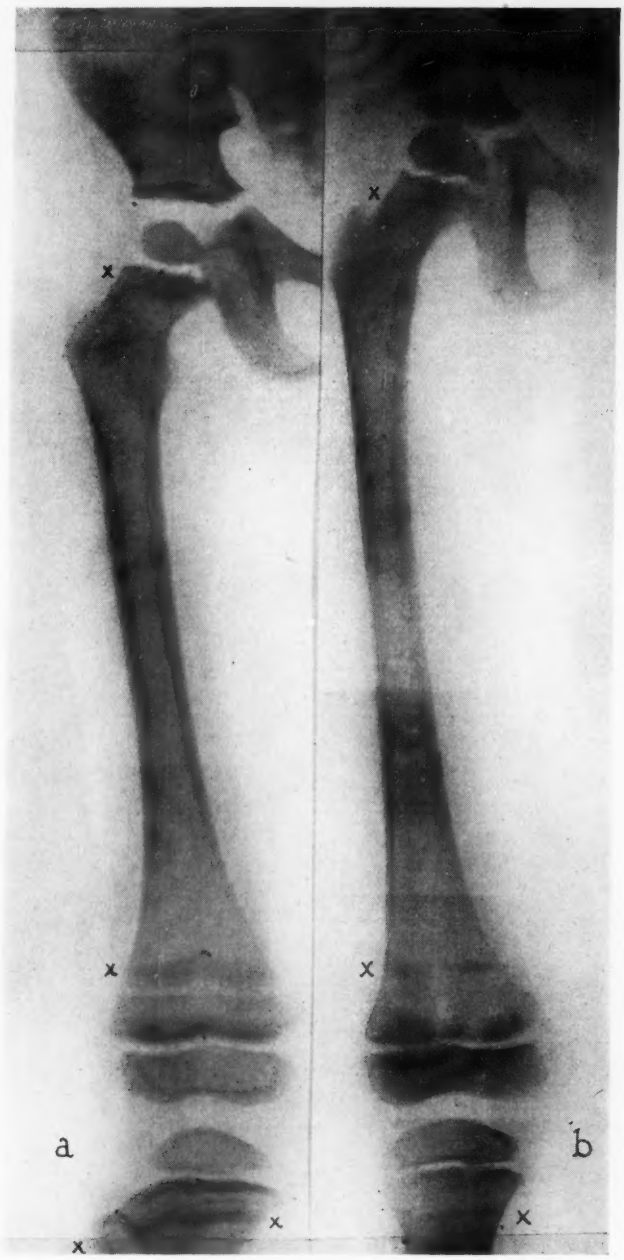

FIG. 1.—Proportions of growth at ends of femur as indicated by heavy bands (*x*) from (*a*) about one year of phosphorus medication in a four-year-old child, and (*b*) a period of malnutrition in a seven-year-old child.

than in those of the rest of the body, as estimated by comparing sitting height with lower extremity length. Then follows a progressive retardation of growth until bony fusion of epiphyses and diaphyses is accomplished.

The fundamental cause of skeletal growth as with the growth of all tissues lies buried in a heap of biologic reactions as yet very little understood. It is known that much is inherited in the germ plasm and usually can be altered but little. It is also known that mechanical forces, as those resulting from muscular action and gravity have an important influence on bone growth. In addition there are the specific chemical forces that are active in the endocrines and the nutriments as well as in various acquired disorders that influence skeletal growth. In a given case it is often difficult or impossible to evaluate the part played by one or more of these factors in control of growth. An example of bone growth determined by factors in the germ plasm and little influenced by external forces is seen in a case reported by L. Keck.[4] A child, one month old, had a congenital bifurcation of the leg, the tibia, covered by skin and subcutaneous tissue being in one compartment, and the fibula and foot with all the muscles in the other. Despite the absence of muscular action on the tibia its size and shape approached fairly near to the normal. While the tibial growth was not greatly retarded by the absence of the play of static-cinematic forces upon it, the fibula was definitely stimulated by them as shown by transverse growth hypertrophy especially in its lower half.

Fell and Robison[5] have made significant observations of inherent growth tendencies in the skeletal anlagen. They studied the growth of five and one-half to six-day-old embryonic chick femurs *in vitro* by explantation into plasma and embryo extract for periods varying from three to 27 days. The five and one-half-day-old femurs were short thick rods of cartilage with rounded processes representing head and trochanter proximally and condyles distally. There was a rapid increase in length of shaft and in diameter of the epiphyses with approximation of the normal shape of the femur despite the fact that there was no play of forces exerted by soft parts upon the explant. Ossification occurred along the surface of the middle portion of the shaft of some of the oldest specimens. Thus, a markedly inherent capacity of the embryonal femur for both growth and differentiation was displayed. C. B. Huggins, J. Exp. Med., has quite recently observed similar continued growth of the vertebrae of the tail of the young rat when they are transplanted free in its abdominal cavity.

In general it appears that longitudinal growth of the bones of the endoskeleton through cartilage is less influenced by the removal of mechanical stimuli than is transverse growth through fibrous tissue. Thus, in case of marked loss of function of limb from infantile paralysis or ankylosis from Still's type of chronic arthritis, the shafts may continue to increase in length and the epiphyses to enlarge at a rate that is only moderately under normal, while at the same time the transverse growth of the shafts may be much retarded or even arrested. This is illustrated by a roentgenogram of the knee region of a 12-year-old girl with Still's disease of several years' duration

(Fig. 2). In this case retardation of growth was also complicated by atrophy of disuse in which there was concentric absorption of bone along the periosteal surface of shaft which actually reduced the diameters of the bones, especially the fibulae. The bony centers in the growing epiphyses having over their sides a surface covering of cartilage the cells of which do not become phagocytic

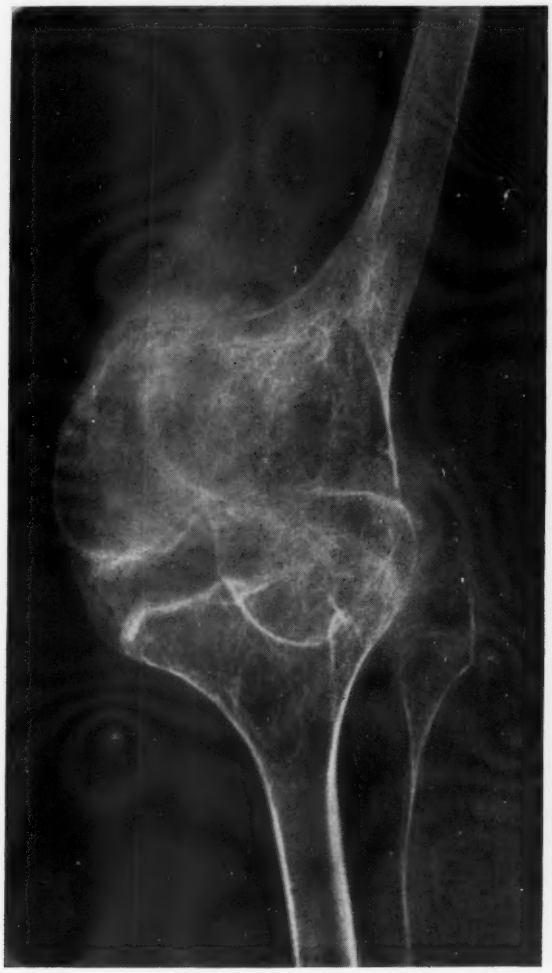

FIG. 2.—Retardation of transverse growth and concentric atrophy of disuse of shafts in Still's arthritis in 12-year-old girl. Epiphyses not reduced in size. Note the large epiphysis in contrast to the narrow shafts which were only slightly shorter than normal.

during periods of disuse are not subject to concentric atrophy and consequently never decrease in diameter.

Osborne and Mendel,[6] and Winters, Smith and Mendel[7] found that rats have a growth potential that may be slowed up during the period of restriction of certain foods or inorganic salts, but after restoration of an adequate diet the loss is soon made up. However, the skeleton is not retarded in longitudinal

growth by the dietary deficiency. But one difference between rat and man is that the epiphysial lines remain open and longitudinal growth continues throughout the life of the rat, whereas they close in man between the 12th and 22nd years, according to the epiphysis concerned. And it is known that while prolonged nutritional deficiencies as of vitamin D during the growing period of man usually produce only temporary retardation, they may result in an undersized mature skeleton, as witnessed in the case of rachitic dwarfism.

Endocrines and Bone Growth.—Of the glands of internal secretion, the hypophysis, the gonads, the thyroid and the parathyroids are the ones that are known to influence skeletal growth, in some cases directly, in others indirectly.

The secretion of the anterior lobe of the hypophysis augments bone growth. Overfunction in man causes gigantism and delayed closure of epiphysial lines, provided it begins before normal growth is complete and acromegaly provided it begins afterward. This view is supported by animal experimentation. Anterior lobe extract injected into the rat whose epiphysial lines never close, produces gigantism (Evans and Long[8]), while in adult dogs it produces acromegaly (Putnam[9]). Also it is found that tumors destroying the anterior lobe of the hypophysis and beginning before closure of the epiphysial lines cause delayed closure and pituitary dwarfism. Hypophysectomy in young animals causes dwarfism, the retardation of growth of the bones and testis being more marked than that of the other tissues. Feeding such animals anterior lobe extract causes them to grow, indicating that the growth stimulating hormone is formed there (P. E. Smith[10]). It is assumed that the eosinophilic cell secretes the growth promoting principle because pituitary gigantism and acromegaly are nearly always produced by an eosinophilic adenoma.

The effect of the gonads on bone growth is less well known. Castration and congenital or acquired hypofunction of gonads delay the time of closure of the epiphysial lines sometimes for a great many years which establishes the possibility of longitudinal growth beyond the usual span. In some cases it seems to continue and mild degrees of gigantism may result as in case of some of the "Skopzen" (members of a Russian religious sect practicing castration) studied by Tandler and Gross.[11] But in the great majority of cases there appears to be no further growth and height does not exceed that of the average adult.

Growth retardation with delayed puberty may occur in case of prolonged infectious disease during childhood and adolescence. It is seen especially in severe tuberculosis of the spine or hip. Three such male patients have recently been observed in our orthopedics clinic in which at the ages of 17 to 20 the skeletal and testicular development was approximately that of 12 to 14 years. It is problematical as to how the infection delays growth, but it may be by depressing the hypophysis, which secondarily affects the bones and testicles. One patient came to autopsy at the age of 20, at which time the epiphysial lines were open and the testicles which were small showed no spermato-

genesis. Fig. 3 shows him at the age of 17 years and Fig. 4 the delayed bone growth at 19 years.

Hypofunction of the thyroid gland as seen in cretins results in dwarfism during the normal period of bone growth and in persistence of the open epiphysial lines sometimes to well past middle life. Slight longitudinal growth may continue during adult life, but it never makes up the deficiency. Excision

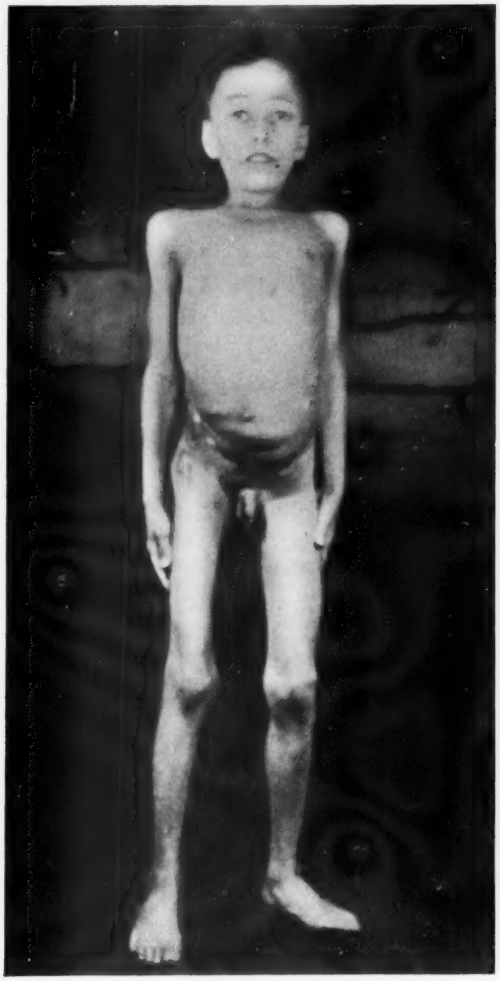

FIG. 3.—Delayed puberty and retarded bone growth in 17-year-old boy with long standing tuberculosis of spine.

of the thyroid in young animals as rabbits not only dwarfs the skeleton but makes it porotic or pseudorachitic.

Evans[12] believes that the thyroid secretion probably affects bone growth only indirectly by its action on the anterior lobe of the hypophysis. Thyroid subnormality depresses pituitary function, *i.e.*, the thyrotropic pituitary hormone resulting in cretinic dwarfism. Smith[13] found that the growth stimula-

tion which resulted when rats from which hypophysis, thyroid and parathyroids had been removed were injected with anterior pituitary growth hormone was increased if thyroid extracts were also administered.

Bone growth during hyperfunction of the thyroid (thyrotoxicosis) has not been studied in children, except for relatively short periods and almost entirely after the tenth year. Aub and coworkers[14] have observed osteoporosis with increased excretion of calcium and probably of phosphorus in adults but there is little evidence that permanent underdevelopment of the skeleton results from juvenile thyrotoxicosis. The effect of prolonged overfeeding of thyroid to young animals has not been accurately determined. According to DaCosta and Carlson[15] large doses usually produce a diarrhea, emaciation and death in a relatively short time. But the feeding of small doses to rats beginnings at the 18th to the 21st day and continuing for as long as 100 days produced no apparent change in size of the animals.

Chronic parathyroid deficiency following goiter operations with removal of parathyroid tissue has not been reported in children, but in adults it has not resulted in changes in the bones. Dr. L. R. Dragstedt has recently found that the bones of a young dog subjected to thyroparathyroidectomy followed by thyroid administration, continued to grow normally until killed after eight months despite the fact that the blood calcium ranged steadily between five and one-half and six and one-half mg. and the phosphorus between five and six mg. per 100 cc. Hammet,[16] however, found slight retardation of growth of bone in rats after parathyroidectomy. On the other hand a continued excess of parathormone in the blood, whether from injection in animals (Bodansky,[17] John-

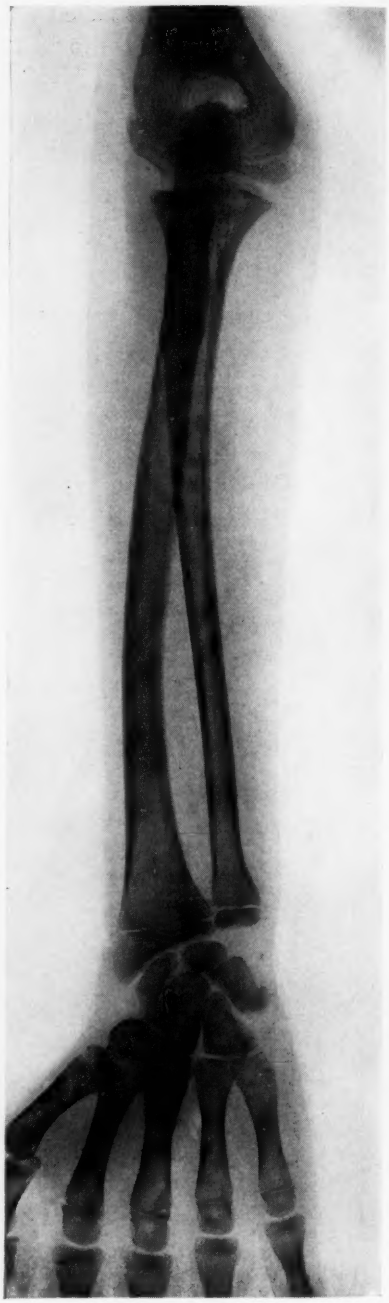

FIG. 4.—Roentgenogram showing delayed bone growth of patient in Fig. 3 at age of 19 years.

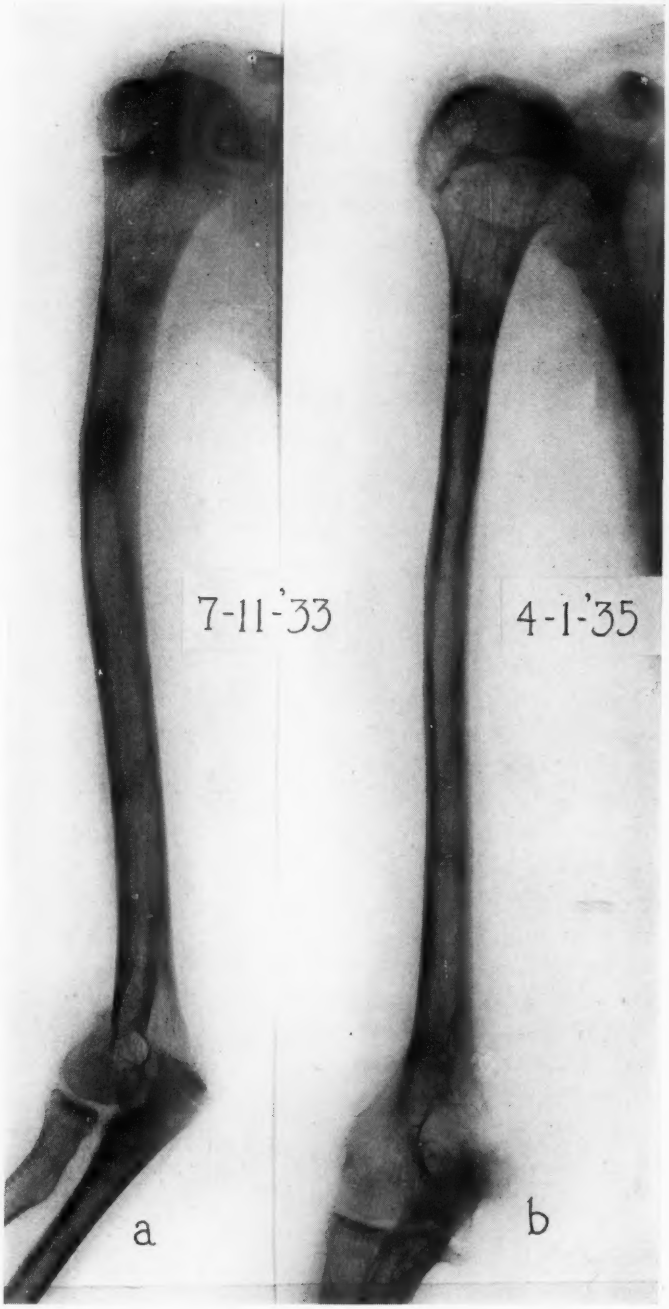

FIG. 5.—Hyperparathyroidism. (*a*) Shows humerus at age of 11 years and four months; (*b*) at 13 years. There has been increase in length of shaft and in diameter of epiphyses during the interval but reduction in diameter of shaft.

son and Wilder[18]) or from parathyroid tumor results in withdrawal of calcium salts from the bones and hypercalcemia. In the seven reported cases of parathyroid tumors with hyperparathyroidism in children there has been little said about bone growth but osteoporosis has been a constant finding, cysts and giant cell tumors being absent. I have recently observed a case on the pediatrics service of the University of Chicago Clinics in which there was withdrawal of calcium from the bones, but despite this there was continuous, although atypical growth of the skeleton. A 13-year-old girl gave a history compatible with parathyroid tumor of about three years' duration. Two and one-half years before admission this diagnosis had been made elsewhere and one and one-half years before she had been examined in this clinic. The blood then contained 16½ mg. of calcium and 2.5 mg. of phosphorus, per 100 cc. and roentgenograms showed osteoporosis with little relative change in dimensions of the bones. There was evidence of a healed fracture of the right humerus which occurred one year before. On readmission the blood calcium was 16.9 mg. and phosphorus 2.4 mg. per 100 cc. Fresh roentgenograms showed marked generalized osteoporosis with actual reduction in diameter of the shaft of the right humerus whose neighboring shoulder joint was restricted in motion by calcium deposits about it (Figs. 3, 4 and 5). The shafts of the other long bones were approximately of the same diameter as in the previous roentgenograms. On the other hand, all bones had increased in length and the bony centers of the epiphyses were considerably increased in diameter. This shows that despite the presence of osteoporosis, enchondral bone growth went on in the epiphyses and at the ends of the shafts, yet transverse growth of shaft by fibrous ossification was practically suspended.

The sympathetic nerves appear to play no special rôle in bone growth. Cannon and co-workers[19] observed unaltered growth after total excision of the sympathetic chain on either one or both sides in young cats. Bisgard[20] observed no difference in the hind limbs of growing goats after unilateral excision of the lumbar ganglia and no acceleration of growth from the same procedure carried out on the paralyzed side of a monkey with experimental poliomyelitis. On the other hand Harris[21] reported increased longitudinal growth after lumbar sympathectomy in cases of retarded growth in one leg from poliomyelitis. But muscle regeneration might play a rôle in such cases.

Plasticity of Growing Bone.—A substance as hard as bone is naturally thought of as possessing a considerable degree of stability. But physiologic hardness and biologic plasticity are attributes that do not run counter to each other. In fact, a growing bone is in a constant state of structural change which concerns the metaphyses most and the cortex in decreasing amounts away from the ends. The ends of the shafts increase in length and at a much slower rate in diameter by the laying down of bone in the epiphysial line. This is followed by a reduction in diameter of the shaft and an increase in thickness of the cortex at a decelerating rate away from the epiphysis; also, by a continuous realignment of trabeculae in the cancellous bone of the ends of

the shaft and to a much less extent in the epiphyses. Narrowing of the diameter of the ends of the shaft is accomplished by absorption of bone along the periosteal surface by mononuclear and polynuclear cells, while new bone is being laid down along the medullary surface by the process of fibrous ossification. Within, old trabeculae are being absorbed and new ones continuously formed to meet the shifting lines of force. The haversian, circumferential and interstitial systems of lamellated bone are constantly being added to as the shaft increases in length and thickness. There is more or less creeping replacement of old living bone by new bone as form and function change with growth, much as in the case of replacement of dead bone by new bone to be discussed later. The seat of greatest osteogenic activity in transverse growth of shaft between the metaphyses is along the periosteal surface. This plastic process gradually comes to an end as maturity is reached and is finally replaced by the slow balanced process of tearing down and building up which is concerned with the normal metabolism of adult bone.

Bone Repair.—Bone repair in its broadest sense includes the healing of either a general or a local impairment of the skeleton regardless of the causative agent. While the subject of general repair is one of great importance in the wider aspects of medicine and biology it is the narrower implications of local repair that are of special interest to the surgeon. Local damage of bone may vary much in cause and severity and the reparative response may vary accordingly. Thus, accidental trauma, operation, inflammation and neoplasm all produce their own types of lesions, and the healing reaction of each shows the special imprints of the causative factor.

Bone repair is seen in its simplest form as the reaction to uncomplicated injury to which this discussion will be limited. As it occurs in nature this is nearly always a fracture. In the repair of a fracture, nature's problem is to restore bony structure in such a way that normal function may be resumed. The trauma fractures the bone, tears or strips periosteum, produces a hematoma and damages ends of fragments sufficient to kill osteocytes for a variable distance back from the fracture line. Function is interrupted because of pain and loss of mechanical support. The tissue fluids of the injured region also undergo biochemical changes. These alterations in structure, function and chemical composition are followed by a reparative reaction, the morphologic aspects of which are better known than the physiologic. They consist essentially in the formation of a callus which eventually becomes bone and in the removal of the tissues that undergo necrosis. The unossified tissues that are active in the normal growth of bone especially periosteum and fibrous tissue of the marrow canal are thrown into much greater activity in the process of repair. In addition to these fixed tissue cells there are wandering and infiltrative cells, the lymphocytes, monocytes and macrophages, that are sufficiently metaplastic to take part in the formation of the callus. The first tissue formed invades the blood clot and consists of cells that morphologically are indistinguishable from the fibroblasts seen in the repair of other wounds. Harvey[22] is of the opinion that fibroplasia is the first step in the repair of all tissues

derived from the mesenchyme. Various factors have been held to initiate this reaction. A biophysical one is the disturbance in the static equilibrium of the cell with its environment by the trauma causing it to revert to the spherical form which gives the most efficient ratio of cytoplasm to surface area. This disturbs the ratio of cytoplasm to nucleus and sets up cell division, thus restoring the balance.

Carrell and Baker[23] attribute growth of these primitive cells in tissue culture to chemical agents in the media formed by the break down of damaged cells by autolysis. They are the higher split products of certain proteins, which, when partly digested, caused marked acceleration of growth when added to tissue cultures. The higher split products of fibrin were especially active. This raises the old question of the possible stimulating action of the fibrin in the blood clot of the fracture on the callus (Potts[24]). Since there is necrosis of bone in the fragment ends for a variable distance back the question arises if growth stimulating substances are formed by autolysis of its proteins which help to bring about creeping replacement of the dead bone by new bone. Since the work of Gudernatch[25] has shown that certain amino acids as arginine and cystine stimulate growth when fed to tadpoles and others more complex as tyrosine, histidine, and diodo tyrosine, which is closely related to thyroxin, stimulate differentiation, the view is strengthened that products are liberated in the hydrolysis of proteins of the dead tissue which stimulate callus formation.

Subsequent changes in this fibrous callus vary according to whether it is periosteal or endosteal in location. In any case it is sufficiently embryonic to undergo extensive metaplasia as emphasized by Downs and McKeown.[26] If endosteal it is gradually transformed into cancellous bone by direct or fibrous ossification, cartilage never appearing in the process. If periosteal it goes through a much more complex process of metamorphosis as it changes into bone. There is partially reversion to the enchondral process of bone formation somewhat similar to that of longitudinal growth and partially fibrous ossification. As the callus grows its peripheral portion consists of young proliferating fibrous tissue usually covered by the thickened outer layer of periosteum. Beneath this there is formed, after six to ten days, a layer of hyaline cartilage which increases in thickness toward the end of each fragment and forms the bulk of the peripheral intermediary callus. Along the surface of the cortex of fragment end new bone begins to form in four to six days and ossification extends peripherally, gradually converting the cartilaginous callus into a bony one as the fibrous callus is converted into a cartilaginous one. The ossification of the cartilaginous callus in the thickest part of the periosteal portion and in the intermediary portion is by enchondral bone formation similar to that seen in the epiphysial line, but with much shorter columns of cartilage and with faintness or absence of the zone of calcification. But the ossification of some of the cartilage, particularly in its thinner portions away from the fracture line, is by direct change of young cartilage cells into osteocytes, as pointed out by Zondek.[27] Other portions, especially at the limits of the callus, ossify only by fibrous bone formation.

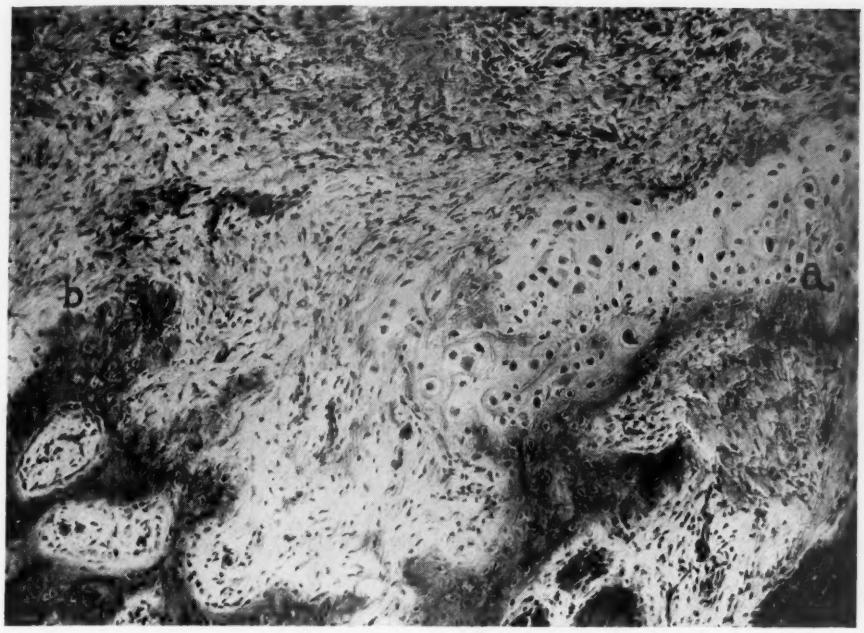

FIG. 6.—Peripheral callus of 17-day-old fracture showing enchondral ossification (*a*), fibrous ossification (*b*), and superficial fibrous callus (*c*).

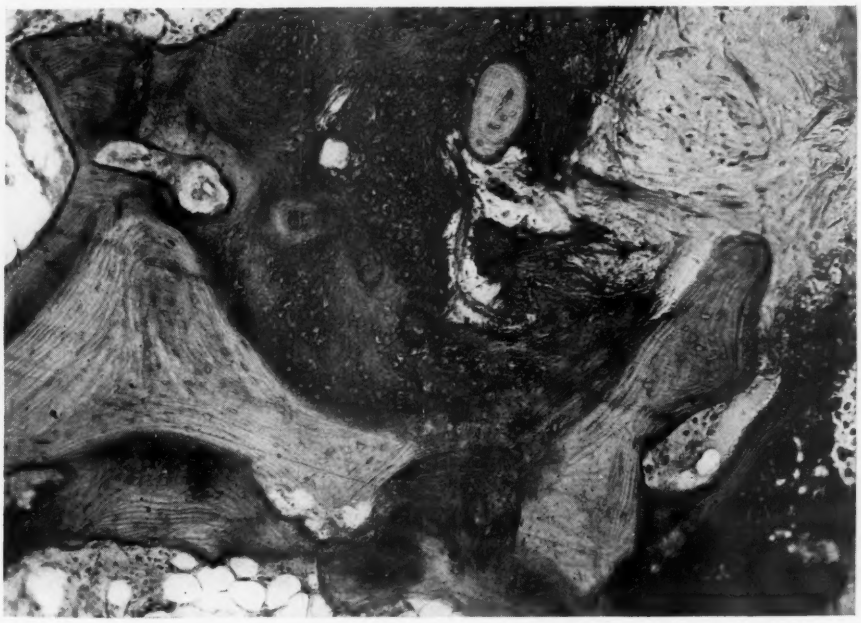

FIG. 7.—Calcification and metaplasia of mature fibrous tissue into bone in fragment end of ununited fracture of four years' duration.

Figure 6 is of a 17-day-old peripheral callus from a fractured ulna of a man. It shows both fibrous and enchondral ossification occurring in neighboring regions.

The peripheral bony callus becomes dense in its superficial portion and spongy in its deeper portion and old cortex may be partly absorbed as callus condenses and diminishes in size. The intermediary callus is always the last to ossify and failure results in delayed or non-union. The initial fibrous callus is very plastic in its later differentiation. It gives rise not only to cartilaginous and bony callus but also to fatty and hemopoietic bone marrow. Old fibrous callus that has organized into mature fibrous tissue may, under appropriate stimulation, slowly ossify by calcification and gradual metaplasia into bony elements (Fig. 7). This is similar to the metaplasia sometimes seen in tendinous or ligamentous ossification.

The breaking strength of the bone, demonstrated experimentally by McKeown, Lindsay, Harvey and Howes,[28] is restored to normal in somewhat less than double the time of completion of ossification of the callus and before it is fully transformed into compact bone.

The compact bone that dies in the ends of the fragments is gradually invaded by blood vessels and osteogenetic tissue from the contiguous living cortex and replaced by new bone by the process of creeping substitution as shown in Fig. 8, which is of a fragment end resected because of non-union of the femur 137 days after fracture. New blood vessels and fibrous tissue invade the canals. The dead bone is absorbed by mononuclear and occasional polynuclear osteoclasts and replaced by fibrous tissue, marrow and vessels. After the absorption has advanced to a certain point a stimulus for ossification comes into play and new bone is deposited on parts of the walls of the dilated canals in successive layers or rings while absorption is continuing in other regions. Weakening of the dead supporting structure beyond a certain point may cause metaplasia of osteoclastic cells into osteoblasts. In some regions it is a question if the new bone deposited on the old does not then proliferate and destroy and directly replace the old; that is, it is also osteoclastic. The changes are similar to those which take place in the transformation of the dead cortex of a bone transplant. The lime salts of the dead bone undergoing creeping replacement may be to some extent redeposited in the replacement bone. If so, it is very limited as the great mass of lamellae are deposited concentrically away from the old bone and in the field about the blood vessels. The amount of necrosis occurring in the ordinary case does not seem to interfere with bony healing. In fact, the necrotic bone has been regarded by some authors, as Lexer,[29] as a stimulus to bone formation. Hemopoietic and fatty marrow always form by metaplasia at the same time that new bone is laid down.

In case of fracture of bones bordering extensively on joints, as the neck of the femur, the carpal navicular and the astragalus, the blood supply to an entire fragment may be cut off. In that event it will undergo necrosis in mass. An analysis of a series of cases of intracapsular fracture of the neck

of the femur (Phemister[30]) has shown that this occurrence greatly predisposes to non-union of the fracture. Thus, in 49 cases there was death of the head in 32 cases with non-union in 28 of them, while in the 17 cases in which the head remained alive, there was non-union in only nine. The dead fragment, in the event either of union or non-union, is gradually invaded by blood vessels and embryonic connective tissue. A process of creeping substitution of the dead bone by new bone is then set up, which, after several months or years, may terminate in complete replacement by new bone. Fig. 9 shows a bisected necrotic head which was excised four and one-half years after fracture because of non-union. Its white central portion consists of

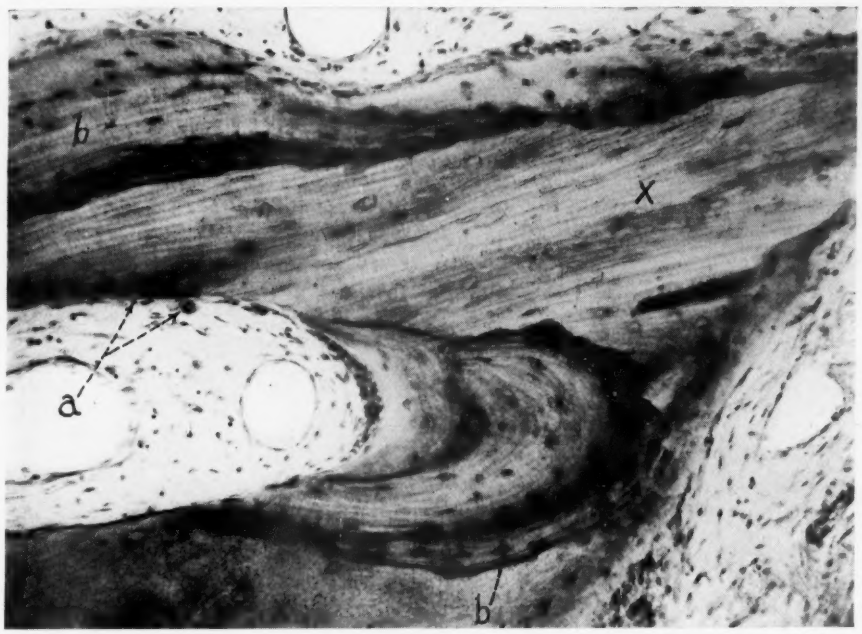

FIG. 8.—Necrotic cortex (*x*) of end of fragment of a 137-day-old ununited fracture. Absorption by mononuclear and polynuclear osteoclasts (*a*) has gone on and new bone (*b*) has been deposited in parts of the dilated canals.

dead bone and marrow, but its grayish periphery consists of living bone which has gradually replaced dead bone. Fig. 10 is a microscopic section at the junction of the dead and living portions showing the fibrous zone of transformation. However, if the fracture unites and the dead bone is subjected to much weight bearing during this period it may collapse at the point of greatest pressure, which occurrence not only interferes with the process of creeping replacement, but also greatly deforms the articular surface.

When bone is transplanted or when a splinter is completely detached, in case of fracture, practically all of its osteocytes die. But, if it is placed in line of bony support, its surviving unossified fibrous elements in its cancelli and canals and along the surfaces usually produce new bone which helps to unite it to the adjacent bone and to replace the dead bone.

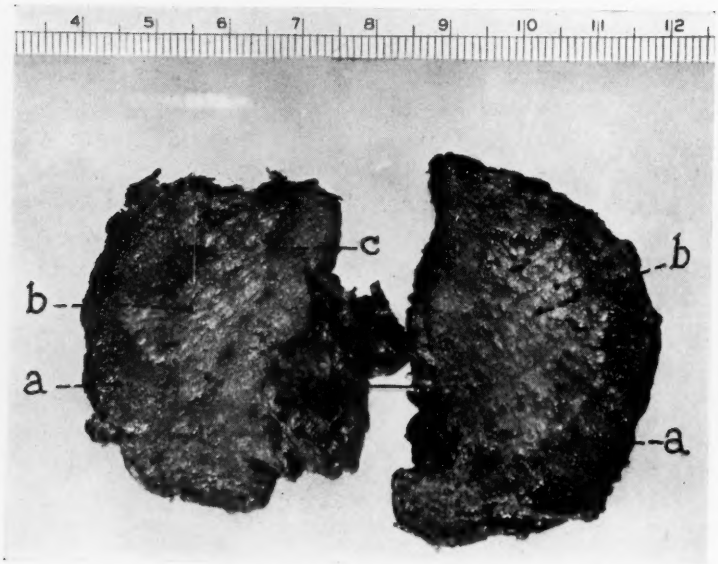

FIG. 9.—Bisected dead head of femur in case of non-union of neck fracture. Grayish peripheral portion replaced by new bone (*a*); white central portion dead and unchanged (*b*); zone of transformation (*c*).

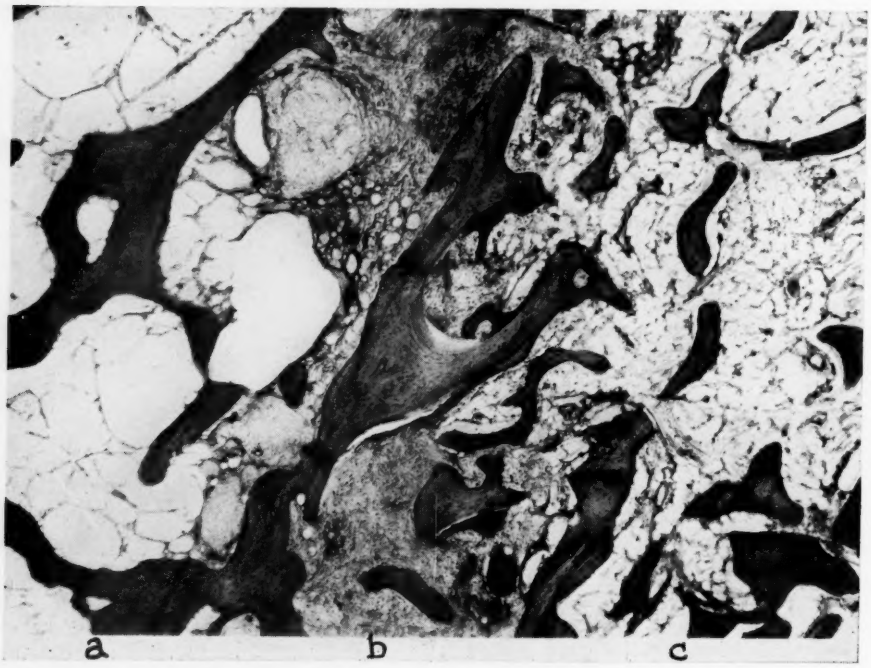

FIG. 10.—Photomicrograph taken through junction of dead and living portions at (*c*) Fig. 9. (*a*) Shows central dead bone, (*b*) the zone of transformation, and (*c*) the new replacement bone.

The debated question as to the rôle of the periosteum in fracture healing is one that should not go without mention, much as one might wish to avoid it. There can be little doubt from both clinical and experimental evidence that the less the periosteum is disturbed the more quickly and surely the fracture heals. It has been my experience that open reduction and stripping of periosteum with or without fixation of fragments by means of any material except an autogenous bone graft is followed by delayed or non-union oftener than when a corresponding degree of reduction and external fixation are obtained by the closed method. Experimentally excision of periosteum from the fragment ends delays callus formation and ossification (Haldeman[31]). These facts indicate that the connective tissue outside of bone and periosteum does not function as efficiently as the periosteum in the process of healing of a fracture.

The same is true in the healing of experimental bone defects (Phemister[32]). Subperiosteal resection of bone in young animals is followed as a rule by moderate to complete restoration of the missing segment, especially when there is a splint bone present to maintain position and fixation. Subperiosteal resection in adult animals is followed by some regeneration, but it is usually very incomplete. On the other hand, resection of an entire segment of a bone with its periosteum at any age results in failure of regeneration. These same conditions apply roughly in man when resections are performed because of the presence of disease, although severe infection, as osteomyelitis in the field of subperiosteal resection by killing osteogenetic cells may restrict the amount of regeneration. In the sloping removal of large areas of the shaft in the treatment of chronic osteomyelitis—the so-called saucerization operation—the stripped off periosteum sometimes forms a layer of new bone in children and young adults that soon fills out most of the defect, thereby defeating the purpose of the operation which was to have it filled by the soft parts. Painting the inner surface of periosteum with a caustic chemical, as formalin or Zenker's fluid, reduces or destroys its osteogenic power, as shown by Van Allen,[33] following rib resection in thoracoplasty.

In segments of the extremity that possess two bones, retardation or failure of regeneration of one that is damaged will set up a compensatory transverse enlargement of its healthy associate. The process is one of very rapid growth initiated to restore function and it continues until a balance is established between capacity of muscles to act and bones to support.

In reverse manner, bone placed out of line as a result of healing of a fracture in malposition, so that its function is diminished or completely suspended undergoes retrogressive changes. Thus, a long projection of a fracture into soft parts may be completely absorbed in the course of time. Detached bone displaced into the soft parts at first usually proliferates along its periosteal and endosteal surfaces and a fracture through such a displaced piece may heal. But after this initial repair the bone undergoes attrition and slowly decreases in size, sometimes to the point of total disappearance. Thus (Phemister[34]) a large fragment of cortex of fractured tibia was dis-

placed posteriorly in the soft parts. The fracture healed and function was restored to normal but a roentgenogram taken six years later revealed almost complete disappearance of the fragment in the soft parts.

Venous stasis produced by ligation of the femoral vein slightly hastens the healing of fractures and regeneration of excised short segments of the fibula, as shown by Pearse and Morton.[35] Sympathectomy has practically no effect on the healing of a fracture, either when carried out at the time of fracturing, or, as McMaster and Roome[36] showed, when the bone is fractured as late as eight months after the sympathectomy. Administration of ductless gland hormones has not been definitely shown to have any effect on the healing of fractures, whether the healing is normal or delayed, except parathormone, which delays healing. Fractures in neglected hyperparathyroidism or von Recklinghausen's disease are predisposed to non-union. On the other hand, parathyroidectomy (resulting in hypocalcemia) has been shown also to delay bone repair by Erdheim,[37] Ross[38] and Speed, Rider.[39] But it has not been shown, either by animal experiment or clinical observation, that deficiency of the other endocrine secretions influences fracture healing. Calcium or phosphorus administration has not been definitely shown to hasten the healing of fractures. However, Brunschwig[40] has administered calcium gluconate to six patients with multiple osteoclastic carcinoma metastases and in two instances marked bone formation in the carcinomatous regions has occurred similar to that sometimes seen following roentgen ray treatment. On the other hand, diets deficient in calcium only have been shown by Downs and McKeown,[41] and McKeown, Harvey and Lumsden[42] to retard fracture healing to a very slight extent. Kernwein, in our laboratory, has studied fracture healing in fasting rabbits receiving only physiologic salt solution. A fibrous callus formed in normal time but there was slight retardation of conversion into bony callus in animals living 25 to 34 days, at which time the controls showed high grade to complete ossification.

Vitamin D has been found by several observers, as Fisher and Key,[43] not to hasten the healing of fractures in normal persons on normal diets, and not to prevent atrophy of disuse accompanying a fracture. And it is well known that fractures in rachitic and osteomalacic patients usually heal in about normal time. There is some disposition to delayed and non-union in cases of osteogenesis imperfecta, but, in general, local bone repair shows a high degree of independence of general body reactions.

Nature of Ossification.—We now come to a discussion of the nature of the process of ossification which is the same in both growth and repair. In the formation of bone there are three essential elements to take into consideration: the cells, the organic matrix, and the lime salts. The oldest and most widely accepted theory of ossification since the establishment of microscopic anatomy is that it comes about somehow as a result of the activity of cells. Certain cellular components of the bone or of membrane which precedes it, as a result of qualities, either inherent or acquired, through the circumstances of their environment, lay down a matrix of collagen fibers

and cement which are chemically and morphologically similar to those of white fibrous connective tissue. Very soon they play a part in the deposition of lime salts in the matrix. Some of these cells become incorporated in the lime salts and mature into osteocytes. Others persist as such along the surface of the bone as do the cells in fish bone, none of which are incorporated in the matrix. Still other cells metamorphose into the components of bone marrow. In some instances as in the ossification of tendon or of the insertions of muscle or fascia to skeleton, there is a conversion into bone of mature fibrous connective tissue. And some observers, as Macewen[44] and Weidenreich,[45] maintain that in enchondral ossification the liberated cartilage cells take part in bone formation. Thus, the cell theory of ossification implies a high degree of specific activity which is either inherent in the cell or transmitted to it by an altered environment.

In contrast to this is the humoral theory of ossification recently propounded by Leriche and Policard[46] and sponsored by others, as Murray.[47] According to it no specific activity is necessary on the part of the cell. All connective tissues having a matrix of collagen fibers and cement serve the purpose equally well. No such claim has been made for elastic tissue or reticulum. The changes that bring about ossification are initiated in the tissue fluids of the matrix by extra cellular substances. They consist essentially in the creation of a local acidity and the establishment of an available local source of calcium salts. This combination results in supersaturation of the tissue fluid and precipitation of calcium salts in the matrix with the creation of bone. There is no discussion of the difference between calcification and ossification and of how the complex morphologic changes in ossification are brought about. In local bone repair, as the healing of fractures, the increased local acidity which, according to Stirling,[48] lasts about one week, is created by local tissue necrosis, the hematoma, and local circulatory stasis. The local source of available calcium is created by the local death of bone and the adsorption of calcium by the fibrin of the hematoma.

Against this humoral theory is the fact that some connective tissue cells possess greater osteogenic properties than others. The existence of a specialized osteoblast is proved by the occurrence of ossification of the metastases of osteogenic sarcomas in the soft parts, as the lungs, lymph nodes, and skin (Brunschwig[49]). Fig. 11 is a roentgenogram and Fig. 12 a microscopic section of an ossifying metastasis in the skin of the face from an ossifying sarcoma of the upper end of the humerus. Extensively ossified metastases were also found in the lungs at autopsy (Bone Sarcoma Registry No. 335). The metastatic tumor cell possesses the osteogenetic property. No local tissue action could possibly account for this. In my opinion most of the ordinary growth and repair of bone is accomplished by cells within and immediately on the surface of bone that have more ossifying tendency than the connective tissue cells outside of bone. However, under circumstances of altered environment connective tissue cells that normally do not ossify may change in character, and become osteoblastic. And there is a dif-

ference in ability of different connective tissues to form bone in the same altered environment. Thus, Huggins[50] has shown that fascia can be made to ossify if it is placed in contact with proliferating urinary tract epithelium, whether the fascia is transplanted to the bladder, or the epithelium is transplanted to fascia or both fascia and epithelium are transplanted together into the spleen. On the other hand, Huggins showed that certain other connective tissues, as that within the spleen, which is largely reticulum or that of bladder wall which is largely white fibrous, do not ossify when in contact with proliferating bladder epithelium. Also a free transplant of fascia will not ossify when mixed with lime salts and placed into a fresh defect in bone, as shown by Key and by Stewart.[51] This latter finding is strong evidence against the theory that any connective tissue will ossify if simply in a field with a low pH and an adequate local supply of calcium. Haldeman and Moore[52] showed that a local excess of solid calcium salts implanted at a fracture site made practically no difference in fracture healing.

As to the low pH in the fracture field resulting from tissue damage it is admittedly present only while the fibrous callus is forming, *i. e.*, during the first week, so that another explanation would have to be found for holding the calcium locally during the important period of ossification which occurs later. And as to the damaged local bone being the source of the calcium that is deposited in the periosteal and endosteal callus, the idea appears far fetched, if one studies fracture healing microscopically or even in roentgenograms, because the amount of dead bone at the fragment ends is relatively small and the signs of absorption of it appear too slight to account for all of the calcium deposited in the callus.

However, in the process of creeping replacement of dead bone or a similar calcareous deposit by living bone, whether in a transplant, boiled bone, or calcified necrotic tissue, it is possible that the local supply of calcium is the source of that which is deposited in the new bone. Bone growth has not been explained by anyone by such changes as Leriche and Policard hold responsible for bone repair.

According to Cameron and Moorehouse[53] blood plasma and the tissue fluids each hold about the same amount of calcium which is present in both crystalloidal and colloidal solution, part of the calcium being ionized and part un-ionized. An important recent discovery is that calcium carbonate and tricalcium phosphate do not exist in bone as separate deposits, as was long supposed, but in chemical combination as a double salt $(CaCO_3)$ X $Ca_3(PO_4)_2$ in which X is usually 2. This substance as found in nature is known as dahlite. The discovery was made by roentgenographic spectral studies of bone by DeJong, Taylor and Sheard and Roseberry, Hastings and Morse.[54] There are no lines present in roentgenographic spectograms of bone which correspond to crystalline calcium carbonate and tricalcium phosphate has never been prepared in crystal form, according to Taylor and Sheard.[55]

Hastings[56] has formulated the arrangements favorable for bone forma-

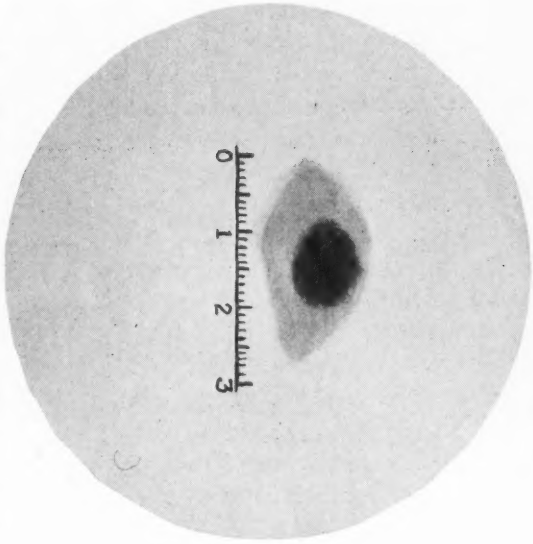

FIG. 11.—Radiograph of ossified sarcoma metastasis in skin of face from osteogenic sarcoma of humerus.

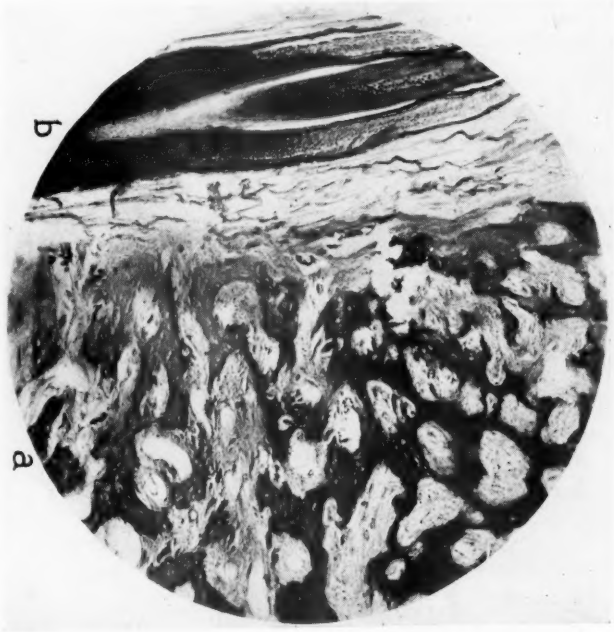

FIG. 12.—Photomicrograph of tissue shown in Fig. 11. Tumor bone (*a*), about hair follicle (*b*).

tion as follows: (1) Optimum physical conditions for the surface precipitation of calcium salts on surfaces which are provided by newly formed fibrils and cement; and (2) optimum chemical conditions which are provided by the existence of calcium ions, phosphate ions and carbonate ions in the tissue fluid. In order to have precipitation of the double salt $CaCO_3.2\ Ca_3(PO_4)_2$ it is necessary that its solubility product constant be exceeded. This might be accomplished by an increase in the calcium, PO_4 or CO_3 ions. Then, by the law of mass action governing difficultly soluble salts, the calcium carbonate and the calcium phosphate will be precipitated together.

A difficult question is which of these ions is increased to such a point and how is the increase brought about? The theory of Robison[57] is that the phosphate ions are increased due to the splitting action of an enzyme, phosphatase, upon the esters of hexose phosphoric acid. Such esters are present in the blood and tissue fluids. Phosphatase has been demonstrated in the blood and in the fields of predilection for ossification, as epiphysial cartilage, periosteum and membrane which preforms bone. Taylor[58] thinks that osteoblasts of bone or connective tissue cells under continuous strain form phosphatase whereby bone is laid down around them. But phosphatase is also present in equal abundance in other tissues, which do not ossify or calcify, as, for example, the kidney. This militates against it as the cause of ossification. That phosphatase may be present in tissues for purposes other than to promote the precipitation of calcium salts has been suggested, but not yet established. Taylor thinks that in the kidney it is active in phosphate excretion. On the other hand, while less probably so, a local increase in number of carbonate ions could be responsible for the dahlite precipitation in bone and an enzyme (carbonase) might be the agent which brings it about.

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THE TREATMENT OF TUBERCULOSIS OF THE SPINE IN YOUNG CHILDREN

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THE surgical treatment of tuberculosis of the bones and joints was a natural step in evolution with the development of aseptic operative technic. The results of the early attempts to accomplish permanent cure of bone and joint tuberculosis by complete or partial excision were discouraging. These early operators were working under the false impression that they could eradicate the disease by such surgery and were not primarily interested in an improved method of splinting the joint involved. Such surgery was not successful and gave way to treatment by immobilization in plaster jackets and braces. Observations of large series of cases over long periods of time brought out two important facts. First, tuberculous joints without surgical interference show little tendency to heal (actually may persist, though relatively quiescent, for as long as 50 years) and, second, when nature effects a cure the joint is usually firmly ankylosed.

The modern approach to the treatment of bone and joint tuberculosis includes first of all a recognition of the need for rest of the body as a whole and in particular of the joint or joints diseased. No apparatus which has been used, and this includes the most accurately applied plaster jacket or brace, can give immobilization which is comparable to satisfactory fusion of tuberculous joints (Fig. 1).

The leading proponents of the treatment of tuberculosis of the spine by means of adequate immobilization through an arthrodesing operation have been Drs. Fred Albee and Russell A. Hibbs. Both of these surgeons have had an experience with this procedure over a period of more than 20 years. The patients have been accurately studied and follow up procedures have been carried out. In 1930 Albee[1] included in his review the report of 181 cases of children who were under ten years of age when operated upon. No detailed analysis of this particular group was made, but in the entire series of 865 cases operated upon, the result in 90 per cent was classified as excellent or good. Hibbs[4, 5] reported the results of spine fusion by his method in 210 cases. Of this group 98 were ten years of age or under at the time of operation. The percentage of patients cured or markedly improved was approximately the same as that reported by Albee.

Although the excellent results reported by Hibbs and Albee did appear to justify the general adoption of this procedure, there have been many objectors to operations upon children under 12 years of age. This study of the treatment of tuberculosis of the spine in young children was undertaken because of dissatisfaction throughout this country and in Europe with the results obtained by attempts at fusion of the immature spine.

In 1927, Kidner[7] reported a series of 14 cases of children under 12 years of age, seven of whom were operated upon and seven treated exactly the same but without operative interference. He concluded that cases in which fusion was done required practically as long and careful after treatment as those without operation. His treatment covered a period of three to four years and consisted of Bradford frame and plaster jacket. Some of his cases were kept recumbent one and one-half years after operation.

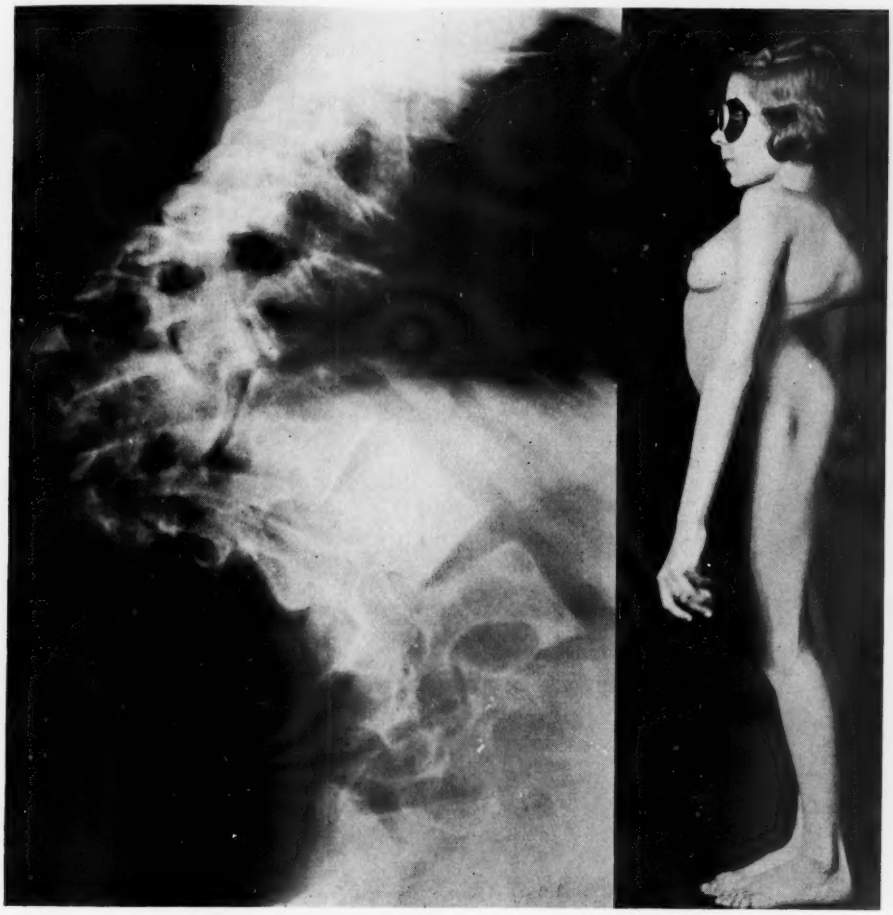

FIG. 1.—The result of "conservative treatment" for a period of 14 years. The spine has healed but, although the patient was treated in a sanatorium by means of plaster jackets and shells, this extreme angulation of the spine developed.

Allison[2, 3] attempted to arthrodese the spines of a group of young children several years ago but soon abandoned the procedure. Other operators using a technic copied after Hibbs or Albee have not been able to duplicate their results.

John L. Porter[9] operated upon a series of ten spines using the Albee technic of a thick bone graft placed in a gutter made in the spinous processes. After six years he was unable to note more improvement than in a group of

unoperated spines. He admitted that his failure might be due to faulty technic.

Kleinberg,[8] after five years in charge of 100 cases of joint tuberculosis in children, felt that a fusion should be done only if repeated flareups occur after three or four years of conservative treatment. In 1920 the Commission of the American Orthopaedic Association reviewed the subject and arrived at much the same conclusion.

FEASIBILITY OF SPINE FUSION BEFORE PUBERTY

One objection to attempts to fuse, and explanation of failure to produce a satisfactory fusion in young children, has been a prevailing opinion that there was not enough bone in the spinous processes and laminae to obtain an adequate arthrodesis of the spine.

In 1931 we were faced with the problem of finding suitable sanatorium facilities for an increasing number of young children with tuberculosis of the spine. It was obvious that these children would require from three to ten years of hospitalization. If they reached an age approaching puberty without satisfactory evidences of healing, an operation for fusion of the spine would be performed. Doctor Allison had been convinced by his own short series of failures that an operation for splinting the spine in young children was not justifiable. He believed that the failures were due to inadequate ossification in the spinous processes and the laminae of these children.

Embryologic studies were undertaken by Jerome and Compere to determine the age at which ossification of the vertebrae and their various appendages was complete. A study of microscopic sections of the spines of fetuses confirmed the statement of embryologists that ossification begins in the vertebral bodies at eight to 16 weeks. At the time of birth, the vertebrae consist of three pieces, the body and two halves of the vertebral arch, each of which has its own well developed ossification center. During the first year the halves of the arch (the laminae) unite behind, union taking place in the lumbar region and extending up through the thoracic and cervical region. About the third year the bodies of the upper cervical vertebrae are joined to the arch on either side. At birth the vertebral bodies near the intervertebral disks as well as the tips of the transverse and spinous processes are covered by a layer of cartilage. In this cartilage, epiphysial centers of ossification appear at the sixteenth or seventeenth year. Fusion is complete about the twentieth year. The line of suture is visible in the bodies for a year longer.

As a result of these studies, Allison became convinced that previous failures of operative procedures, both in his own hands, and that of others, had been due to faulty operative technic. As a result he encouraged us to begin operative fusion in all cases of tuberculosis of the spine regardless of the age of the patient. We are able to report a short series of cases which we have studied carefully, both before and after operation, during the three years since the new orthopedic center at the University of Chicago was opened.

The operative technic which we elected to use consisted of exposure of the spine, excision of part of the articular cartilage from the articular facets,

chiseling and turning curls and splinters of bone from the spinous process of the laminae laterally across the facets and from one lamina to another. A thick osteoperiosteal graft obtained from a tibia or a full thickness tibial graft with some additional osteoperiosteal strips was placed on the denuded laminae on both sides of the spinous processes. The spinous processes were then fractured and placed shingle fashion on top as an additional layer of bone (Fig. 2). In two of the patients operated upon, rib grafts were used instead of bone from the tibia.

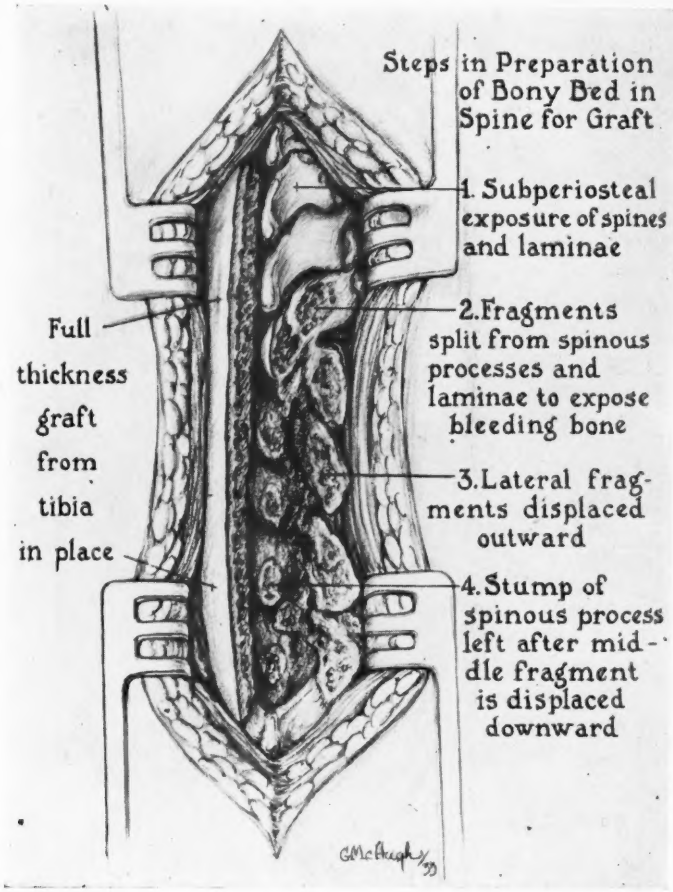

FIG. 2.—Diagram of operation for arthrodesis of the spine in young children.

REVIEW OF CASES

During the past three years we have operated upon the spines of 56 patients suffering from tuberculosis of the vertebral bodies. Twenty-eight of these patients were children 12 years of age or under.

In Table I we have listed 18 cases, ages one and one-half to nine years. There were eleven girls and seven boys. The duration of disease before operation was from six months to five and one-half years. Nine of the patients had been treated by plaster jackets, plaster shells and the usual supportive

measures, including fresh air, and in most instances sanatorium care for more than two years. Eight of the patients had been treated for more than five years. All of the cases still had active disease processes. The patients were malnourished and in two of them there was a well advanced amyloid disease

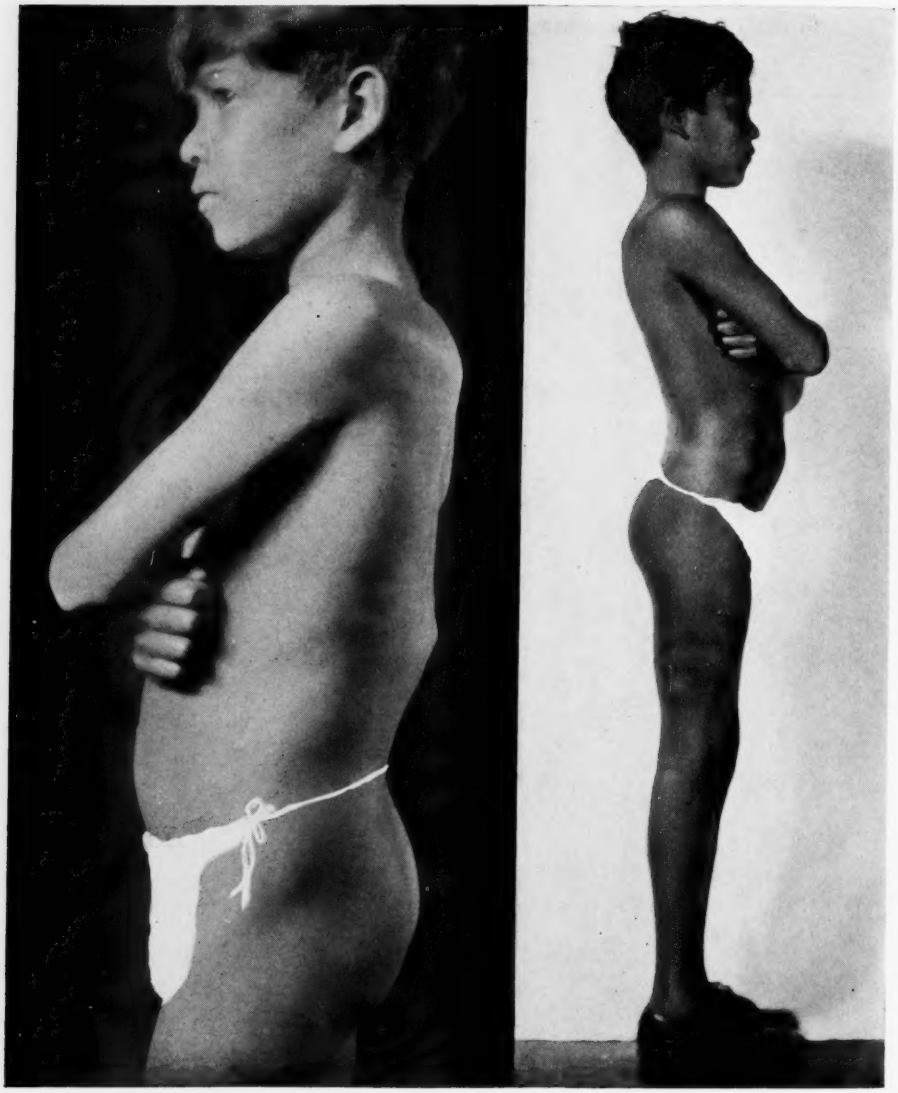

FIG. 3.—C. A., aged 11. The kyphosis was corrected by a turnbuckle plaster cast and the spine was then arthrodesed to immobilize and maintain the correction. Patient is now clinically cured three years after operation.

with draining sinuses which had developed during the period of so called conservative treatment. Onset of the disease in all except one case was at the age of five years or under. The two patients who had an extensive amyloid disease survived the operation and for a time showed improvement. One of them gained 8.0 Kg. in 24 months and the other 2 Kg. in 12 months. This improve-

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TABLE I

Tuberculosis of Spine—Ages One and One-half to Nine Years

Case	Sex	Weight in Kg.				Age at Onset	Age When Operated Upon	Duration before Operation	Present Age	Deformity	Vertebrae Involved	
		Adm.	1-1-34	Gain	Time Elapsed						Level	Number
1. A. K.	F.	22.5	28.0	7.5	35 mos.	3	7	4 yrs.	11	Moderate	D12–L2	3
2. R. M.	F.	18.6	26.0	7.4	31 mos.	8	8	9 mos.	10	None	D 2– 3	2
3. D. Y.	F.	13.2	21.0	7.8	33 mos.	1½	5½	4 yrs.	8	None	L 1– 2	2
4. M. R.	F.	13.0	died	8.0	24 mos.	3	7	4 yrs.	9	Very mild	L 3– 5	3
5. M. B.	F.	16.0	26.2	10.2	31 mos.	1½	6	4½ yrs.	8	Very mild	D11–L2	4
6. W. P.	M.	16.5	died	2.0	12 mos.	3	8	5 yrs.	9	Moderate	D 6–L2	9
7. W. C.	M.	17.5	21.0	3.5	30 mos.	5	6	8 mos.	8	Very mild	D 4– 5	2
8. M. P.	M.	18.5	26.3	7.8	24 mos.	3	7	4 yrs.	9	Moderate	D 8–12	5
9. J. S.	F.	7.2	died	6.0	18 mos.	1	1½	7 mos.	3	Mild	D11–L1	3
10. D. S.	F.	18.5	23.6	5.1	33 mos.	3	5	2 yrs.	7	Mild	D 9–L3	7
11. P. K.	M.	22.0	30.0	8.0	30 mos.	3	8½	5½ yrs.	10	None	D 5– 6	2
12. R. K.	M.	23.0	31.0	7.0	30 mos.	2	6½	4½ yrs.	8	Mild	D10–L1	4
13. J. G.	M.	18.0	27.5	9.5	30 mos.	3½	5	1½ yrs.	8	Mild	D 7– 8	2
14. E. S.	F.	12.0	20.0	8.0	30 mos.	3	3	5 mos.	6	Mild	D 7– 8	2
15. E. J.	F.	13.6	18.5	4.9	18 mos.	1½	3	3 yrs.	4½	Very mild	L 3– 5	3
16. A. J.	F.	12.5	15.8	3.3	22 mos.	2½	3	6 mos.	5	Very mild	L 2– 3	2
17. V. T.	F.	17.0	17.5	0.5	12 mos.	6½	7	6 mos.	7	Moderate	T 9–11	3
18. R. K.	M.	11.8	12.6	0.8	3 mos.	1½	2½	1 yr.	2½	Mild	L 1– 2	2

ment was not lasting and both patients died of amyloid nephrosis. The third death in this group, which also followed a period of improvement with a gain in weight of 6 Kg. in 18 months, resulted from tuberculous meningitis four months after a second operation made necessary by a fracture of the earlier fusion. Each of the other 15 patients in this group showed progressive improvement. All of these are clinically healed at the present time. Deformities which were present have not been corrected but, with two possible exceptions, there has been no increase in kyphosis of the spine following operation. Those patients who were operated on before deformity occurred have not developed any angulation of the spine. All in this group have shown a satisfactory gain in weight.

Table II details the analysis of ten cases of tuberculosis of the spine in patients aged nine to 12 years, inclusive. All of these patients have shown improvement and the deformities which were present at the time of operation have not increased. In two instances we were able, by hyperextension, to partially correct the deformity and in one (C. A.) a rather marked deformity of D12 to L2 was corrected so that the patient has a normal spine curve both from the standpoint of gross appearance (Fig. 3) and in the roentgenogram. These patients have gained from six to 27 Kg. since operation. With one exception, they had been treated from five and one-half to ten years before operation by the so called conservative method of plaster jackets, plaster beds or Bradford frames, rest and the usual supportive measures. In spite of this treatment, the disease was still active, deformities in varying degrees had occurred, sinuses had developed and the patients themselves were undernourished or emaciated. The most striking change noted is that of a boy (L. D.) who, after ten years of conservative treatment, still had a persistently discharging sinus, deformity, and, at the age of 11 years, weighed only 28 Kg. The sinus, which healed within 30 days after the spine was fused, has remained closed. Clinically he is entirely well three and one-half years after operation and able to take part in various types of athletics. Again in this group we note that the number of girls is greater than that of the boys in a ratio of seven to three. The onset of disease in eight of the ten cases was before the age of five years.

There have been five deaths of patients suffering from tuberculosis of the spine (Table III). Two of these patients were not operated upon. One of these (E. H.), aged six years, died of tuberculous meningitis while being treated in plaster shells and the usual supportive measures in preparation for operation. The second (B. C.), died of generalized and pulmonary tuberculosis. One patient, aged three years, with pulmonary tuberculosis and tuberculosis of the spine, died of tuberculous meningitis four months after operation. Two patients who were seriously ill with amyloid disease and marked renal insufficiency at the time of operation survived for 13 months and two and one-half years, respectively, and during the first year or more after operation showed definite signs of improvement from the standpoint of their general nutrition and health. We believe that these two patients' lives could have been saved by an arthrodesis of the spine before renal damage had

TABLE II

Tuberculosis of Spine—Ages Nine to Twelve Years, Inclusive

Case	Sex	Weight in Kg.				Age at Onset	Age When Operated Upon	Duration before Operation	Present Age	Deformity	Vertebrae Involved	
		Adm.	1-1-34	Gain	Time Elapsed						Level	Number
1. E. W.	F.	19.5	28.0	8.5	23 mos.	2	11	9 yrs.	12	Moderate	D 5–10 L 2– 5	9
2. C. A.	M.	29.5	37.0	7.5	24 mos.	11	11	3 mos.	13	None	D12–L2	3
3. L. D.	M.	28.0	55.1	27.0	31 mos.	1	11	10 yrs.	14	Moderate	D 9–L2	6
4. S. S.	F.	22.0	38.5	16.5	30 mos.	3½	9	5½ yrs.	12	Moderate	D 8–12	5
5. R. K.	M.	17.5	28.1	10.6	31 mos.	4	10	6 yrs.	11	Moderate	D 9–L1	5
6. R. B.	F.	32.2	42.8	10.6	18 mos.	3	11	8 yrs.	12	Very mild	L 5	1
7. C. C.	F.	29.0	46.0	17.0	36 mos.	3	11	8 yrs.	13	Moderate	D10–L1	4
8. J. S.	F.	20.0	25.5	5.5	30 mos.	3	11	8 yrs.	13	Moderate	D 8–12	5
9. M. T.	F.	31.0	44.7	13.7	30 mos.	2	10	8 yrs.	13	Mild	D10–L2	5
10. S. W.	F.	21.0	27.7	6.7	30 mos.	7	12	5 yrs.	14	Moderate	D11–L1	3

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become so advanced. At autopsy we found that the spines in both instances were well fused and the tuberculosis of the vertebrae was quiescent (Fig. 4). These two patients had been treated by so called conservative measures and while under treatment they developed persistent draining sinuses. The concomitant amyloid nephrosis had hopelessly damaged the kidneys leading to death from renal insufficiency.

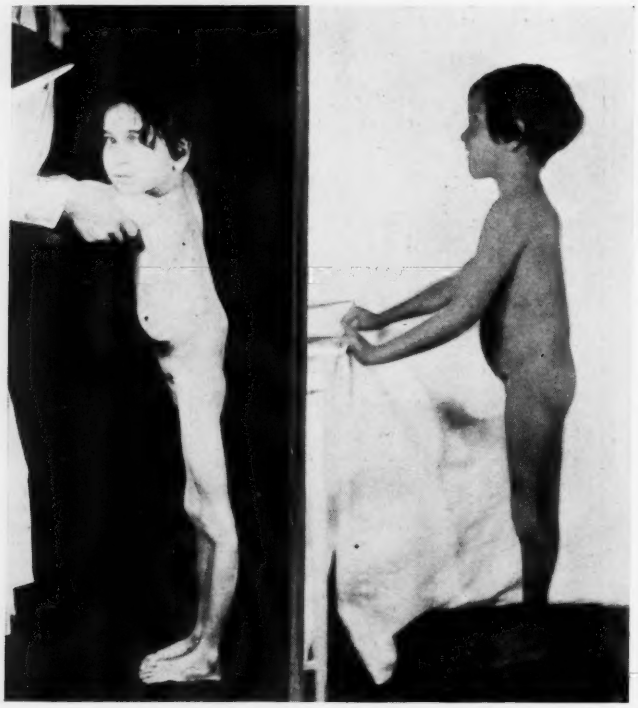

FIG. 4.—M. R., age six years. The clinical improvement continued for two years but, two and one-half years after operation, the patient died of amyloid nephrosis. Necropsy examination showed that the tuberculosis of the spine had been arrested.

TABLE III

Cause of Death

Cases 12 Years and Under When Operated Upon

Case	Cause of death	Age	Time after operation
J. S.	Tuberculous meningitis	3 yrs.	4 months
E. H.	Tuberculous meningitis	6 yrs.	No operation
B. C.	Generalized tuberculosis	12 yrs.	No operation
M. R.	Amyloid disease with nephrosis and secondary infection	9 yrs.	2½ years
W. P.	Amyloid disease with nephrosis	9 yrs.	13 months

In reviewing the series, we find that there were three deaths of patients who were operated upon, two from amyloid nephrosis and one from tuberculous meningitis. Fourteen patients are living and well, apparently entirely healed, 11 patients are definitely improved and have either been discharged

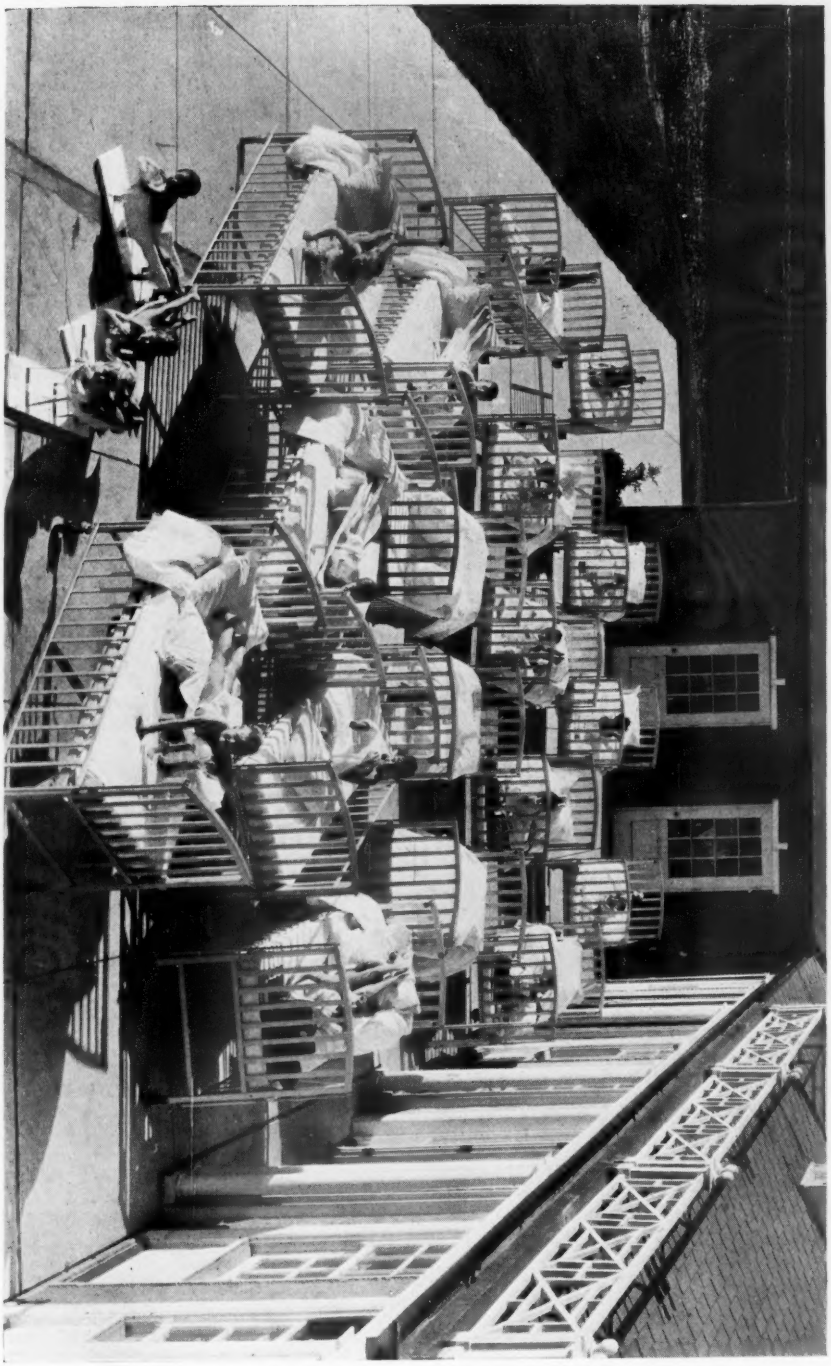

FIG. 5.—Convalescent care of a group of children, all of whom have had operations for tuberculosis of the spine. An anterior and a posterior plaster bed is prepared for each patient.

from our convalescent hospital (Fig. 5) or are ready now for discharge (TABLE IV).

TABLE IV

Number of deaths * (ages 2½ to 12)	5
Number clinically healed	14
Number improved	11
Total	30

* Two of these patients were not operated upon.

SUMMARY

A critical attitude with regard to the advisability of arthrodesing operations in the spines of young children with tuberculosis of the vertebral bodies has been maintained throughout this study. We do not feel that we have had a large enough series or that we have followed these patients for a long enough period of time to be able to state positively that such operations in young children will lead to a cure in any fixed percentage of cases. We are convinced, however, that it is possible to adequately splint the spine in children at any age, even at the time of birth, if the operation is performed carefully; if enough bone is used, preferably full thickness grafts taken from the tibia; and if these grafts are long enough to reach at least two normal healthy vertebrae above and two healthy vertebrae below the diseased vertebral bodies. We are further convinced, from a study of the spines removed at necropsy where death has followed some intercurrent disease or complication, that this splinting is adequate to prevent motion in the joints between the diseased vertebrae and to protect the disease softened vertebral bodies from the trauma of weight bearing. We have also emphasized the importance of adequate supportive measures before and after operation, such as long periods of rest, preferably in plaster shells; high caloric and high vitamin diets; heliotherapy; and fresh air to improve the health of the body as a whole.

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A MODIFICATION OF THE OPERATION FOR SPINAL FUSION

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REFERRING to the operative measures for fixation of the spine, two problems arise which require consideration: (1) The rôle of the graft and of the operation itself. (2) The operative technic and postoperative treatment.

As to the first problem, the opinions of the authors can be divided into two groups. The first, Albee, Tuffier, Ombrédanne, Le Fort, Basset, Haeberlin, Dubois, Dardel, Lauvers, Sebrechts, Schramm, H., Hanson, Maffei, Spišič, Calandra, Courcy, Wheeler, *etc.*, are of the opinion that the bone graft undoubtedly exerts a favorable biologic influence, to the rapidity and completeness of the healing of the specific lesions. The bone transplant is supposed to possess a greater ability of bone production (Albee) than the laminae and to cause a local change in the calcium metabolism and protracted hyperemia. Tavernier suggests some supplementary principle, not closely defined. Leriche, Allenbach, Dieulafé, Juvara and Cocacescu consider that the biologic influence of the graft is probable.

The second, the larger group of authors, Massard, Chevalier, Moutier, Calvé, Galland, Constantini, Bressot, Leclerc, Willmoth, Brandes, Elsner, Deutschlander, Cortes, Llado, Pujoi, Georgesen, Jocobovici, Bristow, Biesalski, Henderson, Delitala, Scherb, Delchef, Minař, Jovčič, Sorrel, Richard, *etc.*, consider the rôle of the graft to be an exclusively mechanical one. The basis for this standpoint is the lack of evidence for the existence of such a biologic influence, the impossibility of comparing and conjecturing the course the case would undergo without a surgical treatment, finally a series of anatomicopathologic examinations of specimens taken from a few months up to a few years after operation, which revealed the existence of unhealed specific lesions in the bodies of the vertebrae, despite the perfect fusion of the transplanted bone.

The study of cases of peri- and paraarticular arthrodesis in cases of tuberculosis of the hip joint leads to the conclusion that the existence of a biologic influence which enhances the rapidity and completeness of healing is undoubtable. This influence is the more remarkable, the closer to the lesion the graft is inserted. Clinically this influence manifests itself by an increased reproduction of bone tissue in the foci, their reduction in size, the rapid union of the bony ends and the rapid recalcification of the entire region. A more profound consideration of these phenomena would require detailed studies. In general the process resembles the phenomena observed in the healing of fractures—active hyperemia lasting weeks and even months, transposition in the contents of calcium salts in the particular parts of the operated region, from the graft

to the diseased tissues, in fractures to the callus—the undoubtable increase in the ability of bone formation in the region of the graft.

All these phenomena take place in that space of time, in which the graft, not being entirely fused, plays no mechanical rôle. Taking the above-mentioned observations under consideration in connection with the measures of fusion of the spine in order to enhance the mentioned biologic influence, the graft should be placed as close as possible to the tuberculous lesions, at least in the sphere of the laminae of the spine.

Referring to the conception of the second group of authors, the mechanical rôle of the graft does not begin until the graft is definitely fused. According to the investigations of Hoessly, Mayer and observations of many others, the definite fusion of the graft does not take place sooner than eight to ten

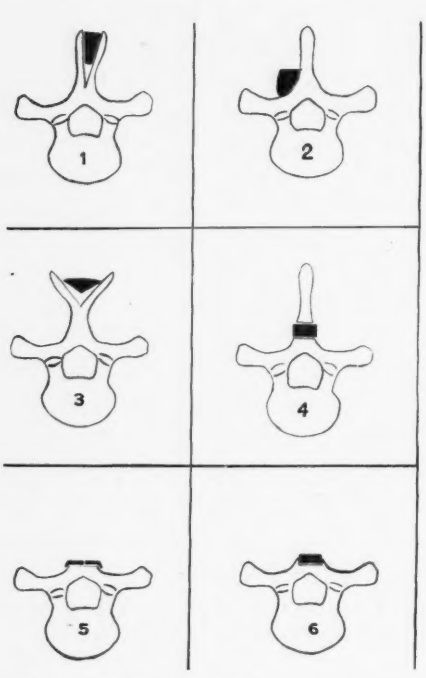

FIG. 1.—The methods of fusion operations of the spine. (After Sorrel.)

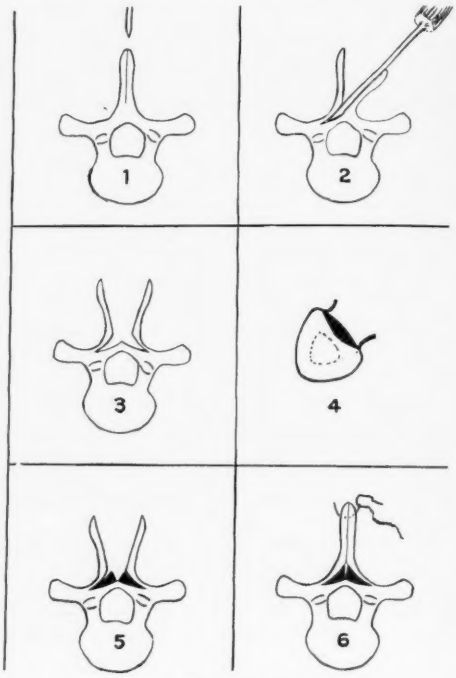

FIG. 2.—The author's method.

months after operation. Four months after operation the graft is the weakest and most liable to break. Therefore the weight bearing of the graft should not take place sooner than five to six months after operation. This standpoint is undoubtedly sound, if the graft is to perform its mechanical rôle.

Certain differences must arise in connection with the different methods of operating. Here we come to the second problem: In most methods, advising autoplastic grafts, the relation between the graft and its bed is for a long time quite loose. The graft is in contact with its base only in some of its parts (Fig. 1; 1, 3, 4), or with one surface only (Fig. 1; 2, 5, 6). Therefore the revitalization of the graft proceeds slowly. Entirely different conditions exist

in the osteoplastic methods such as that of Hibbs and its modifications. Fixation is already strong, when the production of callus takes place, that is six to ten weeks after operation. In these methods, however the biologic influence is insignificant and of short duration as compared with the effect of a free autoplastic graft.

These considerations lead to the conclusion that the classic methods of both Albee and Hibbs should be combined and thus transfer the mechanical point of weight from the autoplastic graft to the callus produced in place. In this way the spine is immobilized within six to twelve weeks after operation.

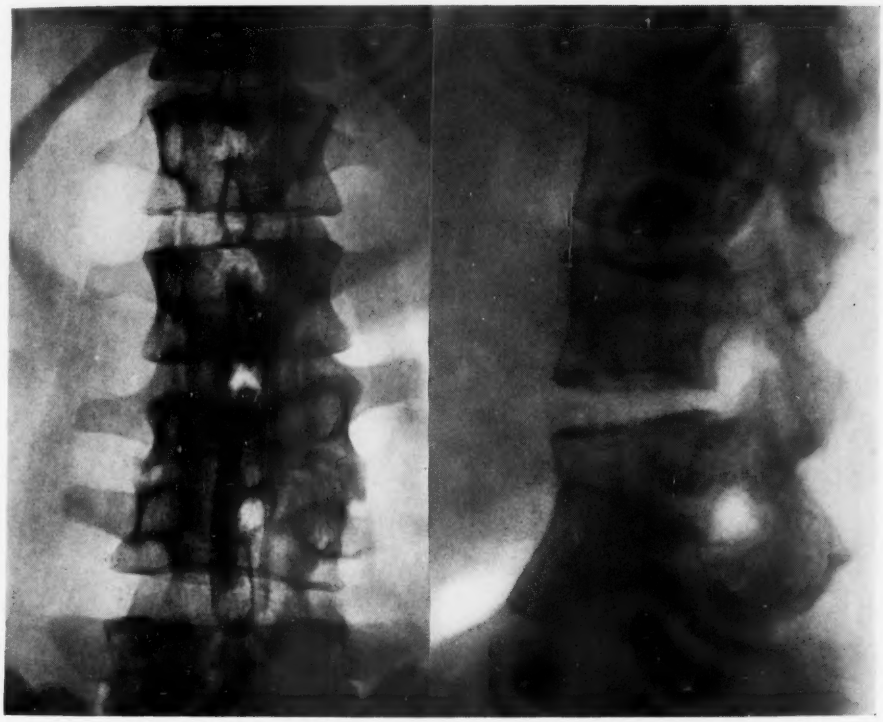

FIG. 3.—(Case I.) Anteroposterior view 16 months after operation. Showing implanted graft and apparent lack of vertebral pathology and smooth strong calcification.

FIG. 4.—(Case I.) Lateral view 16 months after operation. Showing fusion of both vertebrae.

During the subsequent months the firmness of this immobilization will increase, as the fusion of the graft becomes more solid. This has a practical meaning, for the patient may be allowed to walk about and even to perform light work two to three months after operation. The immobilization will be more secure, if besides the fusion of the processes as in Albee's method, or the fusion of the processes and laminae, we also obtain the fusion of the joints of the corresponding vertebrae as in Hibbs' method.

As a result of the above considerations the following operative technic for fixation of the spine has been developed. We operate only upon patients showing a fairly good general condition, prepared by lying a few months in a

plaster of Paris bed and by general treatment. The operation is usually performed under local anesthesia with 1 per cent novocaine.

(1) A semilunar skin incision is made of sufficient length to expose the processes of the diseased vertebrae and one above and below the diseased one. In the dorsal spine two vertebrae above and below. The skin flap is dissected up one cm. beyond the midline.

(2) Incision of fascia, supraspinous, interspinous ligaments and incision of the tips of the exposed spinous processes in the midline, splitting of the processes in halves (Albee's method) by means of a knife chisel, without the use of a hammer to a depth two-thirds to one inch, depending upon the operated region, but it must always reach the base of the processes (Fig. 2; 1).

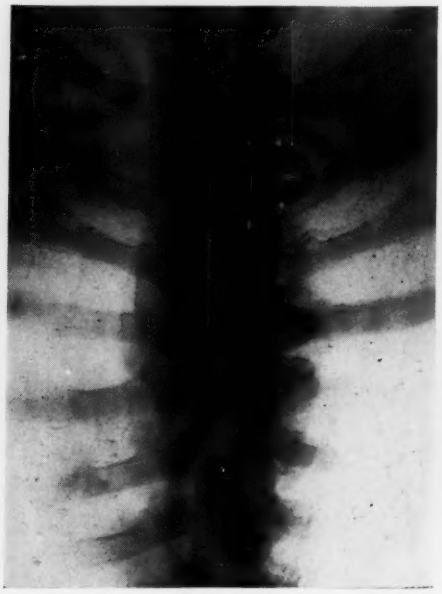

FIG. 5.—(Case II.) Before operation. Showing extent of large abscess in dorsal region.

(3) After all the spinous processes have been thus divided, they are set over to both sides together with the surrounding tissues; a chisel is next inserted at an inclination of 45° and the posterior surfaces of the laminae

FIG. 6.—(Case II.) Before operation. Showing destruction of facing surfaces of ninth and tenth dorsal vertebrae in bone tissue.

are chiselled off as far as the base of the transverse processes in the dorsal spine region, in the lumbar spine as far as the mammillary processes. In the course of the chiseling the whole flap containing one-half the spinal processes and the laminae together with the muscles is retracted laterally and the base carefully trimmed, taking care to produce an abundance of bone chips which remain *in situ* and in the recesses of the wound (Fig. 2; 2). We repeat the same procedure on the other side (Fig. 2; 3).

(4) Into this prepared bed two tibial grafts without periosteum, 1½ cm. wide by 2, 3 or 4 Mm. thick are implanted (Fig. 2; 5). The eventual breaking or splitting of the graft during its procurement is without significance.

(5) The retracted bone and muscles are replaced in their former position covering the grafts and are sutured between the spinous processes (Fig. 2; 6). Next follows the suture of the fascia and skin.

Postoperative Treatment.—Six to ten weeks, depending upon the region operated, in a plaster of Paris bed, then four weeks in a plaster jacket and an orthopedic back brace up to a year.

We have applied this method of operation in 15 cases of tuberculosis of the spine and in two cases of fracture of the spine. The postoperative course was uneventful and mild. In all cases the wound healed by primary intention. One of the patients thus operated upon on account of Kümmel-Verneuil disease five months after a fracture of the spine, was up and walking about the third day after operation, although it was strictly forbidden. This fact, however, did not in the least affect the healing of the wound or the final result.

Illustrative Case Reports

Case I.—F. O., female, aged 19. The family history was negative. Present illness began about three years ago, with complaint of pain on the inner side of the left foot. She was twice operated upon. Seven months later she underwent an operation on account of abdominal hernia. The wound healed by secondary intention. Three years ago there was an abrupt onset of pain in the lumbar region of the spine. The pain periodically intensified and subsided and was present at the time of admission.

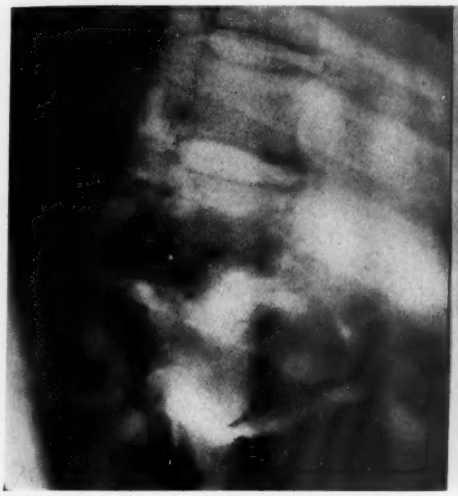

Fig. 7.—(Case II.) Fifty-one days after operation. Showing degree of healing and regeneration in bodies of ninth and tenth dorsal vertebrae at that time.

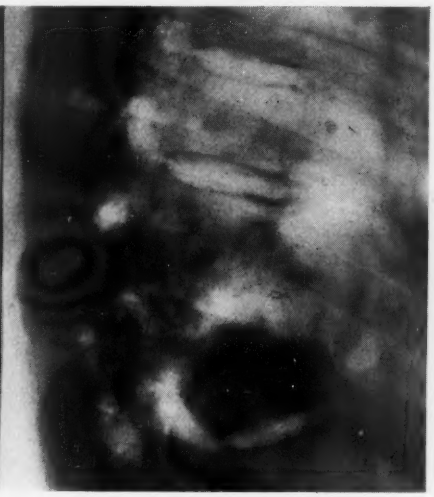

Fig. 8.—(Case II.) Four and one-half months after operation. Showing continuation of reparative process.

Local examination: In the region of the third and fourth lumbar vertebrae a slight protuberance and a mild degree of lumbar lateral curvature. The spinal processes tender to palpation. Pressure exerted along the spine caused pain in the lumbar region. Mobility of the lumbar spine limited. In the left iliac fossa a tumor, the size of a child's head, tender to palpation, fluctuating, smooth surface and not connected with the spleen. Roentgenographic examination revealed extensive specific destruction of the third and fourth lumbar vertebrae.

The patient was treated clinically from 5/12 to 12/12/1931. Her temperature ran up to 39° C. (angina, bronchitis). After this had subsided, she received invigorating treatment and was placed in a plaster of Paris bed. The cold abscess was punctured a few times and the pus evacuated. The patient remained in the plaster of Paris bed until

FIG. 9.—(Case II.) Eleven months after operation.

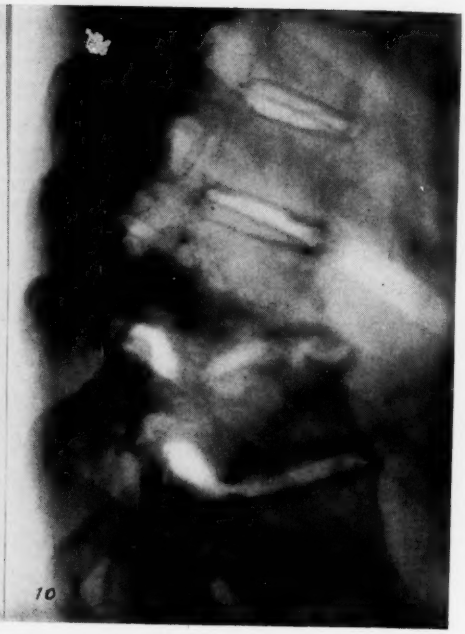

FIG. 10.—(Case II.) One and one-half years after operation.

FIG. 11.—(Case II.) Twenty-two months after operation.

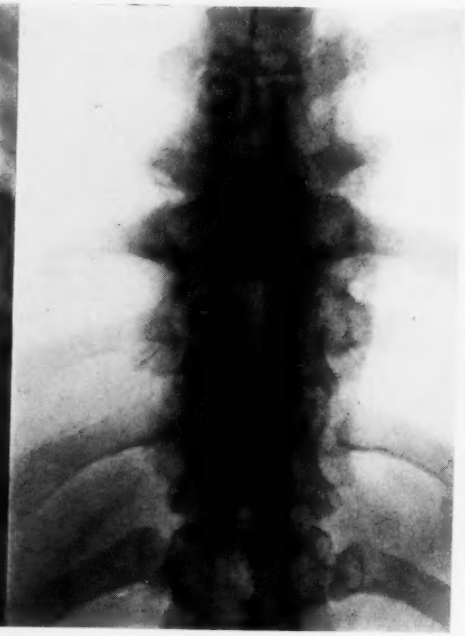

FIG. 12.—(Case II.) Twenty-two months after operation.

May 12, when the described operation was performed. The postoperative course was uneventful. The wound healed by primary intention. June 30 the patient was placed in a plaster of Paris jacket. July 7 she was discharged. The patient removed the plaster jacket after one month, and without any bracing, returned to her work as a servant. A follow up examination 16 months after the operation revealed that the lesions in the spine were healed (Figs. 3 and 4), the general condition excellent and no complaints.

CASE II.—B. S. Diagnosis: Tubercular Spondylitis Thoracalis. Family history was negative. When 33 years of age, after a childbirth she complained of pains in the spine and foot. In the latter a sinus developed. A year later she left for Leysin, where she spent three years. She was given climatic and recumbent treatment. The wound in the foot healed. After her return her condition grew worse. She again left for Leysin, returning after ten months in a deteriorated condition. The pains were considerable, she could not walk and was confined to her bed. She stayed in bed one year before she decided to undergo an operation.

Entrance examination revealed a protuberance and tenderness to palpation and pain on motion in the region of the ninth and tenth dorsal vertebrae. The general condition was good. Roentgenogram showed a destruction of the facing surfaces of the ninth and tenth dorsal vertebrae, with a focus in the bone tissue the size of a plum. The outline of the lesion was indistinct. In the prevertebral space a large abscess was present (Figs. 5 and 6).

December 10, 1932, operation as above. Postoperative course uneventful, except that the temperature, for a larger time showed raised up to 37.3° C.

Follow up roentgenograms every few weeks showed a gradual and rapid filling in of the bone lesions and the reduction of the cold abscess (Figs. 7 and 8). The patient, on her own request, remained in the plaster bed for five months. After the sixth month she wore an orthopedic corset. Follow up examination November 15, 1933: the spine at the level of the affected vertebrae is stiff, the patient has no pain. The general condition is excellent. A roentgenogram shows a highly advanced regeneration and recalcification of the vertebrae. The implanted grafts outline distinctly. The mass of the cold abscess reduced (Fig. 9). The last follow up examination December, 1934, revealed a clinical condition similar to that a year previous. The roentgenogram showed a practically complete disappearance of the foci in the bodies of the vertebrae (Figs. 11 and 12).

The operative method herewith described differs from other procedures in a few features:

(1) It brings the point of action of the operation close to the diseased lesions in the bodies of the vertebrae.

(2) The implanted graft is situated almost entirely within bone tissue.

(3) Fusions of the laminae, joints and the spinous processes proceed rapidly.

(4) The operation does not damage any of the elements normally immobilizing the spine, such as the ligaments, muscles, *etc.*

(5) The biologic influence of the graft, due to its situation close to the foci and within the bone tissue, is rapid, conspicuous, and of long duration.

LIGATION OF VARICOSE VEINS*

AMBULATORY TREATMENT PRELIMINARY TO SCLEROSING INJECTIONS

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FROM THE SURGICAL DISPENSARY AND THE
VARICOSE VEIN CLINIC OF THE
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WITH the increasing popularity of sclerosing solutions, there has been a tendency to neglect essential surgical procedures in the treatment of varicose veins. However, as experience was gained with the injection method, many recurrences were noted. Their number varied from 10 per cent (de Takats[1]) or 15 per cent (Cooper[2]) to 98 per cent of those followed for one year or more (Howard, Jackson and Mahon[3]).

The recurrence usually appears in the patient with large varicosities, in which the valves of the saphenous or of the communicating veins are incompetent. The thrombus produced by the sclerosing solution is not able to withstand the constant hydrostatic pressure from the column of blood in the vein above, which de Takats, *et al.*,[4] found to be as much as 210 cm. of water with the patient standing. This pressure may be increased by coughing, straining at stool, and other actions producing an increase of intra-abdominal pressure. There result then an early canalization of the thrombus and a gradual reappearance of the varicose veins.

It became evident, therefore, that in order to produce a cure in many cases of varicose veins some method should be adopted which would remove the factor of pressure from above upon the thrombus. de Takats[5] was the first in the American literature to call attention to the work of Moszkowicz,[6] who suggested the combination of vein ligation with injections. de Takats believed that ligation was indicated especially in cases where the saphenous was dilated and had incompetent valves above the knee (Trendelenburg +). He was doubtful whether ligation was of value in those cases where the valves of both the saphenous and the communicating veins were incompetent (Trendelenburg ++). His patients were ambulatory throughout their treatment.

Since 1930 ambulatory ligation has been practiced at the Varicose Vein Clinic of the University Hospital. It is the purpose of this paper to report the results obtained in 226 ligations performed upon 178 ambulatory patients.

Indications.—At first ligations were performed only upon recurrences following injection, and upon large veins with incompetent valves of the saphenous and communicating veins which could not be readily treated by sclerosing solutions. The indications for ligation have been extended as experience with the method has increased. Ligations are performed at the saphenous opening on all cases in which the valves of the vein are incompetent (Trendelenburg +).

* Read before the Philadelphia Academy of Surgery, October 1, 1934.

In cases with large veins in which some of the valves of the saphenous are competent, ligation is performed at the highest palpable portion of the vein. The patients are tested by elevation of the extremity and pressure is made at the highest palpable or dilated portion of the vein. If the veins are

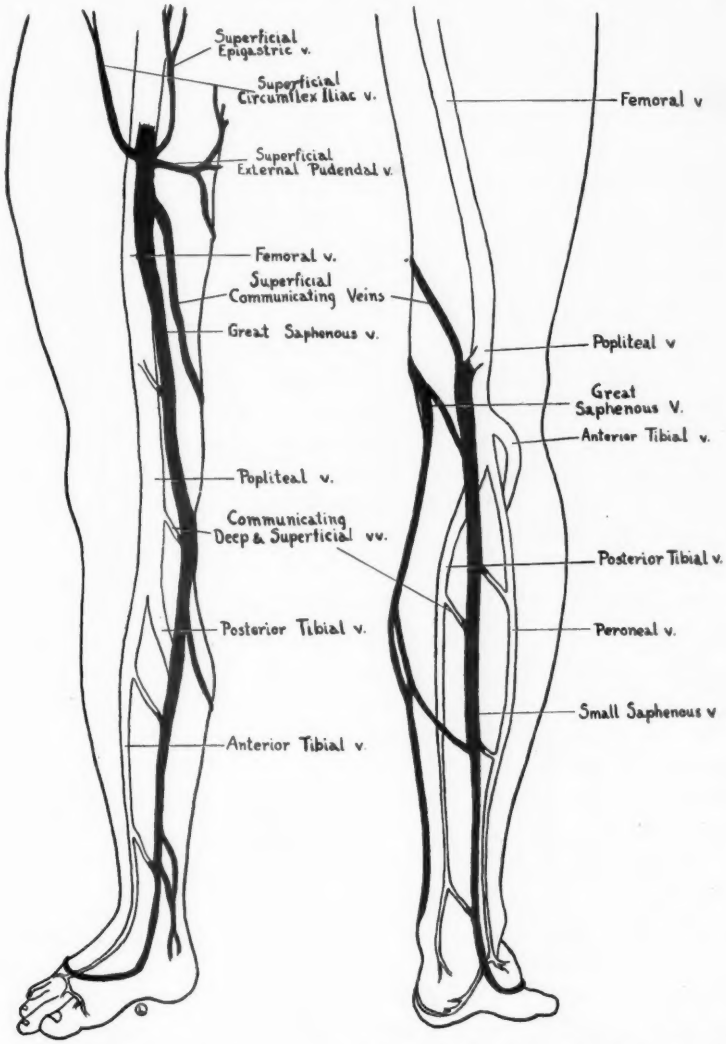

FIG. 1.—Diagrammatic representation of the superficial (black) and deep (white) venous circulations. Note the large anastomosing vessel between the small and great saphenous veins. The superficial circumflex iliac and superficial external pudendal veins at times empty into the upper end of the saphenous as shown and at other times directly into the femoral vein. The communicating veins are much more frequent than are shown in the diagram.

empty when the patient stands but fill rapidly from above when the pressure is released, the vein is ligated where the pressure was applied, whether it be above or below the knee. Ligations are performed on both the long and the short saphenous veins (Fig. 1).

In cases with incompetence of the valves of both the long saphenous

and the communicating veins, the long saphenous is ligated first, and, if the veins below are not readily thrombosed, the communicating branches are ligated where they join the superficial veins.

Ligations are performed upon and no injections are given patients who have a history of a superficial thrombophlebitis within the previous year. Injections are definitely contra-indicated in these cases and relief of symptoms may be safely obtained by ambulatory ligation.

Technic of Ligation.—The operation is a simple one and may be performed under local anesthesia. It is best to mark the site chosen for ligation with some colored solution while the patient is standing. A simple skin infiltration is made with 1 per cent procaine solution containing adrenalin. If the incision is made in line with the vein, better exposure is obtained and a greater length of vein may be resected. The incision should be carefully made through the skin because many veins are found lying attached to the skin with no intervening subcutaneous areolar tissue. As soon as the skin is cut through, small rake retractors are used to produce lateral traction, and the vein is carefully separated from the surrounding tissue by blunt dissection. As soon as possible a curved hemostat should be gently passed under the vein and, by traction, the underlying tissue may be separated from it. To permit easier dissection, the vein should then be divided between hemostats and each end turned back. As tributary branches are encountered, they are also divided between hemostats. It is especially important to find and clamp the branches communicating with the deep circulation. As much of the vein is dissected out as can be removed through an incision one and one-half inches long; often it is possible to remove as much as six or eight inches of a tortuous vein through such an incision. The main branches and tributaries are ligated with plain No. 00 catgut. Occasionally, in large veins, the upper end is doubly ligated. The wound in the subcutaneous tissues is closed with interrupted sutures of plain No. 00 catgut, which are inserted so as entirely to encircle the subcutaneous wound, thereby obliterating all dead space. The skin is closed with vertical mattress sutures of silk. A pressure dressing is applied.

In ligations at the saphenous opening it is well to expose the vein from below. After dividing it between hemostats, traction may be placed upon the upper cut end, making the dissection easier. When the superficial circumflex iliac and superficial epigastric or the internal pudendal veins empty into the upper end of the saphenous instead of directly into the femoral vein, these vessels should be caught and ligated to prevent recurrence through anastomosing vessels.

Postoperative Course.—At the completion of the operation, the patient is permitted to leave the hospital. She is instructed not to go to bed and is permitted to go about her usual duties. Occasionally, on the second or third day, there is some soreness which is due to a progressing thrombosis of the vein below the site of ligation, but the resulting discomfort is easily relieved by supportive elastic bandages. The sutures are removed on the fifth day.

In a few cases, from the third to the fifth day, there is an inflammatory reaction around the wound which readily subsides after the use of 70 per cent alcohol dressings and a supportive bandage. As a rule, following such an ambulatory ligation, there is a thrombosis of the veins below the site of ligation. This thrombosis may be progressive for a week or ten days but by the end of three weeks it becomes stationary. Hence, a period of three weeks is allowed to elapse after ligation before injections are given in the veins which remain.

Review of Cases.—Two hundred twenty-six ligations have been performed on 178 patients in the Varicose Vein Clinic at the University Hospital. The indications for ligation have been as follows:

Trendelenburg positive	131
Trendelenburg double positive	22
Recurrence after injections	11
Ulcer-feeding vein	13
Phlebitis	8

Ligations have been performed at the following sites:

Saphenous bulb	23
Saphenous bulb and leg	1
Midthigh	88
Thigh and communicating veins at knee or calf	15
Knee	44
Calf	37

Some patients have had one ligation on each leg or two or more on the same leg, as shown in the following table:

Ligations per patient	Ligations
Single ligations { right, 74 / left, 44 }	118
One ligation each leg, 24	48
Two ligations same leg, 13	26
Two on one leg, one on other, 2	6
Three ligations same leg, 1	3
Two ligations each leg, 1	4

Age has been no contra-indication to ambulatory ligation.

16–30 years, 15 patients
31–40 years, 53 patients
41–50 years, 45 patients
51–60 years, 33 patients
61 and over, 16 patients

The youngest patient was a boy of 16 and the oldest a woman of 74 years.

Immediate Results.—The immediate results have been good. No deaths occurred. There were three infections of the wound, one of which necessitated bed treatment. One other patient was treated in bed for a time because of a painful descending phlebitis below the ligation. Mild inflammatory reaction about the wound, necessitating alcohol dressings, was

observed in 15 cases. Primary healing was obtained in 223 wounds. All of these patients were ambulatory. Many of them traveled several hours by auto or train to their homes without marked discomfort. The ligation does not keep the patients from performing their usual duties. As a rule, when the patients first stand, particularly on the second day after ligation, there is a moderate soreness which disappears as they walk. This discomfort is relieved if a firm supportive dressing is maintained.

The descending thrombosis occurring after ligation greatly reduces the veins to be treated by injection and the removal of the hydrostatic pressure from above makes the injections much more effective. The combination of primary ligation and secondary injection has therefore proved a more rapid method of therapy for large veins with incompetent valves. At the same time the advantages of ambulatory treatment are preserved.

The results of any treatment of varicose veins must be judged according to the aims of the therapy. These aims vary according to the symptoms to be relieved, which may be classified under three general heads:

(1) Pain and discomfort in the legs.
- (*a*) Pain, especially at the time of menstruation.
- (*b*) Ache after long standing.
- (*c*) Cramps in the legs, especially at night.
- (*d*) Pains and aches in knee and ankle joints associated with varicosities.
- (*e*) Heaviness and easy fatigue in the involved extremity.

(2) Symptoms and signs plainly due to venous stasis.
- (*a*) Swelling in the legs after long standing.
- (*b*) Varicose ulcers.

(3) Disfiguring veins.
- (*a*) Veins causing no symptoms, but treated for cosmetic reasons.
- (*b*) Veins causing symptoms indicated in groups 1 or 2.

In many cases the symptoms fall into two or three of these groups.

Follow Up Results.—A method of therapy for varicose veins cannot be judged solely by the immediate results. These are usually good in all methods. Certainly a follow up period of one year is insufficient to evaluate any method.[5] A recent report of "not a single instance of recurrence" without a statement of the duration of the follow up period is of little value.[2] As a matter of fact, there hardly can be any time limit set for a cure of varicose veins comparable to the five year cure for carcinoma. It is probable that if observations are continued long enough in most patients with large varicosities, there will be a reappearance of some veins. This probability increases with the duration of the follow up period.

The treatments for varicose veins thus far suggested are intended to remove or obliterate the existing varicosities. None of them, however, remove the first cause of the venous enlargement, whether it be hydrostatic pressure from above transmitted through the femoral and other deep veins,

or an inherent familial weakness in the walls of the unsupported superficial veins. Hence, it would seem logical to expect the recurrence of the old veins or the appearance of new venous radicals which have become varicose since the treatment was given.

The results here presented concern ligations performed during 1930 and 1931, three- to four-year results. In practically all cases sclerosing injections were given following ligations.

During this period ligations were performed on 52 patients. Some of these were bilateral operations and in some cases two or more ligations were performed on the same leg. Twenty-six patients representing 37 ligations have returned for follow up examination, and the results are tabulated in the accompanying table. In all but two patients the painful symptoms have been relieved. There were signs of recurrent venous stasis in six patients. There were no enlarged veins in 11 cases. Eight patients had a few small veins in the calf. Six patients had a reappearance of the veins in the calf; before treatment, all of these had very large veins with double positive Trendelenburg tests. The ligations in this group were all at the saphenous opening or upper thigh. The recurrences were entirely in the calf; the veins in the thigh were well closed.

In evaluating these three- to four-year results, it may be said that ligation with subsequent injections was especially effective in relieving the painful and stasis symptoms. Reappearance of the veins in the calf occurred in 14 of the 26 cases, but in eight of these the veins were small and gave no symptoms. They were most marked in those patients who had had large veins with double positive Trendelenburg tests.

Case Reports

THREE- TO FOUR-YEAR RESULTS OF 37 AMBULATORY LIGATIONS FOLLOWED BY INJECTIONS (26 PATIENTS)

Case I.—Male, aged 64. Very large veins to saphenous opening for six to seven years (Fig. 2). Cramps, heavy feeling and swelling. Ligation at right saphenous opening; no injection. Slight immediate reaction. Three years later no pain, no stasis symptoms, recurrence of veins below knee (Fig. 3). Much improved.

Case II.—Female, aged 56. Veins dilated to midthigh for five to six years (Fig. 4). Cramps, ache and swelling. Ligation in left thigh; one injection. Immediate result excellent. Three years later no pain, no stasis symptoms, no veins (Fig. 5). No trouble since operation.

Case III.—Female, aged 41. Veins dilated to midthigh for 22 years. Cramps, ache and swelling. Ligation in left thigh; four injections. Good thrombosis tenth postoperative day. Four years later no pain, slight swelling, and few veins in the calf. Veins appeared after injury to leg one year ago.

Case IV.—Male, aged 43. Large veins of calf "all of life." Easy fatigue, swelling and ulcer. Ligation at internal saphenous below left knee; two injections. Immediate result excellent. Three and one-half years later no pain, ulcer healed and very few veins. This patient is a ship's cook and wears bandage for protection.

Case V.—Male, aged 60. Veins of both legs dilated to saphenous bulb for five to six years (Fig. 6). Easy fatigue, swelling and ulcer. Ligation in right leg; three injec-

tions. Ligation at left saphenous opening six months later; four injections. Immediate results excellent. Three and a half years after first ligation no pain, ulcer healed. Slight swelling of right leg and recurrence of veins below knee (Fig. 7). Patient feels well.

FIG. 2.—(Case I.) Trendelenburg positive. Saphenous vein enlarged up to saphenous opening.

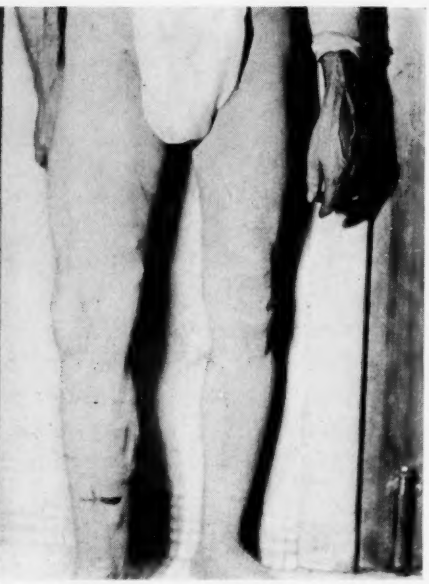

FIG. 3.—(Case I.) Six weeks after ambulatory ligation. The mark on the lower calf shows the lowest level of thrombosis.

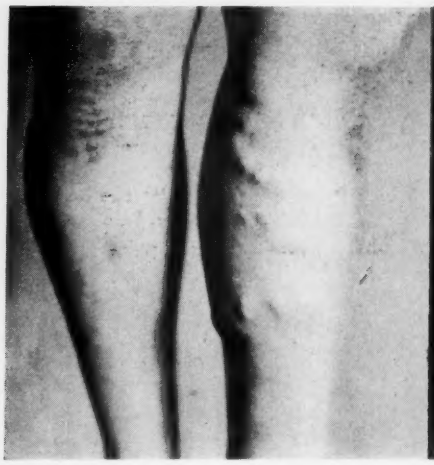

FIG. 4.—(Case II.) Large veins of the calf with double positive Trendelenburg test. Would not thrombose with injections.

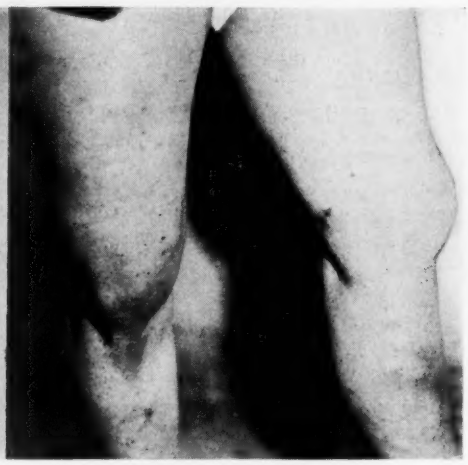

FIG. 5.—(Case II.) Six weeks after ligation and one injection. No recurrence noted at examination three years after ligation.

CASE VI.—Female, aged 57. Midthigh dilatation of veins for 35 years. Pain, cramps and swelling. Trendelenburg double positive. Ligation in upper left thigh, also below left knee on same day; five injections. Slight immediate reaction. Three years later no pain, no stasis symptoms and no veins. Patient works daily as chambermaid.

CASE VII.—Male, aged 54. Large veins to upper thighs for five years. Easy fatigue and swelling. Ligations at left internal saphenous and in right midthigh on the same day; no injections. Patient in bed three days due to extensive postoperative thrombosis. Three years later no pain, no stasis symptoms and no veins.

CASE VIII.—Female, aged 45. Veins dilated to midthigh for 20 years. Cramps, pain and slight stasis symptoms. Ligation in left thigh; six injections. Immediate result good. Three years later no pain, no stasis symptoms and very few small veins. Patient "feels ever so much better."

CASE IX.—Female, aged 36. Smaller veins of calf for three years. Cramps but no stasis symptoms. Trendelenburg double positive test. Ligation in right calf; two injections. Immediate result good. Four years later no pain, no stasis symptoms and no veins. Patient well pleased from cosmetic viewpoint.

FIG. 6.—(Case V.) Referred to clinic wearing truss because of large dilatations at the saphenous opening. Trendelenburg positive. Varicose ulcer, lower left leg.

CASE X.—Female, aged 33. Large veins of long saphenous. Pain with periods, cramps and swelling. Ligation in upper right thigh; no injections. Veins entirely thrombosed. Three years later no pain, no stasis symptoms and some small veins. Patient feels well.

CASE XI.—Male, aged 37. Large veins of calf for 12 years. Pain, easy fatigue and swelling. Ligation at internal saphenous six inches below knee; no injections. Immediate result good. Three years later no pain, no stasis symptoms and no veins. This patient received injections at another clinic.

CASE XII.—Female, age unknown. Large veins to saphenous opening for 20 years. Pain with periods, ache and swelling. Ligation at right internal saphenous below opening;

no injections. Slight immediate reaction. Three years later no pain, no stasis symptoms and no veins. "Right leg is now the better of my two limbs."

CASE XIII.—Female, aged 53. Large cavernous veins for five years. Cramps, ache, swelling and ulcer. Ligations in both legs; four injections. Ligation in left midthigh two years later; two injections. Four years after first ligations no pain, ulcer healed, no swelling and few small veins. Patient much pleased.

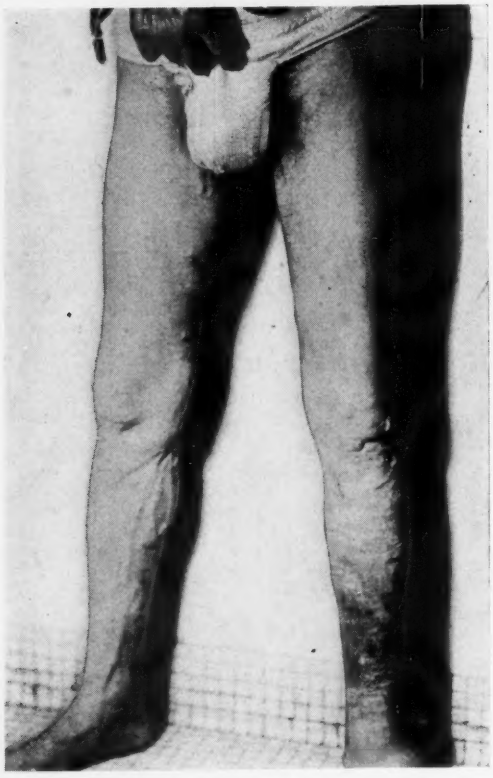

FIG. 7.—(Case V.) Three months after second ligation. Three injections were given in left calf.

CASE XIV.—Female, aged 52. Incompetent saphenous veins. Ache and swelling. Ligation in lower right thigh; four injections. Ligation in left leg about one month later; two injections. Immediate results good. Three years later no pain, no stasis symptoms and no veins. Patient considers herself cured.

CASE XV.—Male, aged 54. Veins dilated to midthigh. Heaviness, ache, easy fatigue and swelling. Ligation in right thigh; three injections. Immediate result good. Three years later no pain, slight swelling and partial recurrence of veins. To have further injections.

CASE XVI.—Female, aged 32. Disfiguring veins in both legs. Ache with periods. Ligation in right thigh; two injections. Ligation in left knee about one month later; one injection. Immediate results good. Three years later no pain, no stasis symptoms and few small veins. To have further injections for cosmetic reasons.

CASE XVII.—Female, aged 30. Moderate dilatation to knee for six months. Pain with periods. Ligation in right thigh; six injections. Thrombosis above ligation. Four years later no pain, no stasis symptoms and no veins. This patient has had several injections scattered throughout follow up period.

CASE XVIII.—Female, aged 49. Veins dilated to midthigh for 12 years. Easy fatigue and swelling. Ligation in right thigh; three injections. Immediate result excellent. Four years later no pain, no stasis symptoms and no veins. This patient feels fine.

CASE XIX.—Male, aged 46. Large veins to midthigh for 30 years. Heaviness, ache and swelling. Ligation in left thigh; five injections. Immediate result excellent with slight redness of wound. Four years later no pain, slight swelling and large veins. This patient had had previous excision of internal saphenous.

CASE XX.—Female, age unknown. Large veins for seven to eight years. Pain, "could not walk a block," swelling, ulcer. Ligation in right calf below knee; four injections. Immediate result good. Four years later no pain, ulcer healed and few small veins. Patient feels much better than before operation.

CASE XXI.—Female, aged 38. Large internal and external saphenous veins for 12 years. Ache, easy fatigue and swelling. Ligations in left thigh and below left knee on

same day; four injections. Symptoms relieved. Four years later no pain, no stasis symptoms and partial recurrence of veins. To have more injections.

CASE XXII.—Female, aged 52. Veins dilated to midthigh for eight years. Ache and slight swelling. Ligation in left thigh; no injections. Four years later no pain, no stasis symptoms and no veins. Patient "had forgotten about veins."

CASE XXIII.—Female, aged 51. Large veins for 15 years. Pain, cramps and swelling. Ligation in right thigh; one injection. Ligation at right knee one year later; two injections. Three years after first ligation no pain, no stasis symptoms and no veins.

CASE XXIV.—Female, aged 38. Large veins of both thighs for 20 years. Pain in legs and swelling. Ligation in upper left thigh; no injections. Ligation in upper right thigh one year later; no injections. Immediate results good. Three years after first ligation pain, swelling and few small veins. This patient had marked thrombosis below ligations.

CASE XXV.—Female, aged 35. Veins dilated to midthigh for ten years. Ache, easy fatigue and slight stasis symptoms. Ligation in right midthigh; three injections. Ligation in left midthigh; five injections. Good thrombosis following ligations. Three years later ache, easy fatigue, slight swelling and partial recurrence of veins. To have more injections.

CASE XXVI.—Male, aged 36. Large veins of calf for four years. Pain, swelling and ulcer. Ligation at left inner knee; five injections. Immediate result good. Three years later no pain, ulcer healed and no veins. This patient has no symptoms.

SUMMARY

In treating patients who have large veins with incompetent valves (the Trendelenburg positive case) injections of sclerosing solutions alone are not satisfactory because of the early canalization of the thrombus caused by the hydrostatic pressure from above.

The indications for ligation preceding injections are the Trendelenburg positive and double positive tests, recurrences after injections, ulcer-feeding veins and phlebitis.

The technic of the operation is simple and may be safely performed on ambulatory patients.

The results of the treatment must be judged according to the symptoms to be relieved and not solely upon presence or absence of veins after treatment.

The three- to four-year results in 26 patients treated by ambulatory ligation and subsequent injection may be tabulated as follows:

Symptoms	Relieved	Recurrence
Painful	24	2
Stasis	20	6
Disfiguring veins	12	8 (few small in calf) 6 (reappearance in calf)

The treatment of large varicose veins by ambulatory ligation followed by injection is recommended as rapid, effective and safe. The end-results compare favorably with those treated by other methods.

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BRIEF COMMUNICATIONS AND CASE REPORTS

AVULSION OF THE SCALP

TREATED WITHOUT GRAFTING

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IN THIS industrial and automotive age it is not uncommon to see patients who have had the misfortune to lose by accident a large area of the scalp. This loss of tissue may or may not be associated with a denudation of the pericranium, and in either instance, presents a trying surgical problem. Usually the forces producing an avulsion of the scalp macerate the tissue to such a degree that its replacement is impossible.

The primary object is hemostasis, treatment of shock and the prevention of infection, since the liberal anastomosis of the emissary veins and sinuses, via the veins of the diploe, may readily result in a fatal meningitis. Dr. John Staige Davis[1] has reviewed in detail the history, etiology, anatomic considerations, mechanism, complications, prognosis and usual methods of treatment employed in avulsion of the scalp. The case herewith presented illustrates an approach in the treatment of extensive avulsion of the scalp without the aid of grafting, and shows what can be accomplished if one appreciates the great degree to which the remaining scalp may be stretched, if mobilized and drawn together in multiple stages, allowing sufficient interval for compensation in the marginal scalp.

CASE REPORT

Catherine F., aged 11, white, entered the Jackson Memorial Hospital, Miami, Florida, June 5, 1933, with a history of having caught her hair in the wringer of an electric washing machine. An extensive area of the scalp covering the crown of the head had been avulsed. Hemostasis was effected, the skull painted with a 5 per cent solution of gentian violet and a pressure bandage applied in the outpatient department. Shock was there combated and antitetanic serum, 1,500 units, administered the next morning. The dressings were changed to continuous wet ones of half strength Dakin solution. Some temperature and serum sickness delayed operative intervention for one week. The denuded area measured 12½ cm. transversely and 14½ cm. in the antero-posterior direction (Fig. 1). Virtually all the pericranium underlying the avulsed area was lost.

June 14, 1933, under basal avertin anesthesia with supplemental nitrous oxide-oxygen, a tourniquet was applied around the head just above the ears and the scalp margins mobilized down to the supra-orbital ridge anteriorly, the occipital protuberance posteriorly, and laterally to the subtemporal fossae. The margins of the remaining scalp were then drawn toward each other by means of mattress sutures through lead buttons,

FIG. 1.—One week after accident, before attempt at closure.

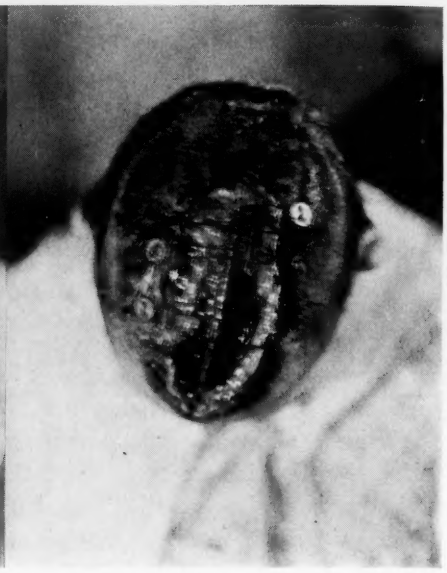

FIG. 2.—Result of first stage, showing lead button mattress suture across rubber tube with reduction of open wound to one-half the diameter as shown in Fig. 1.

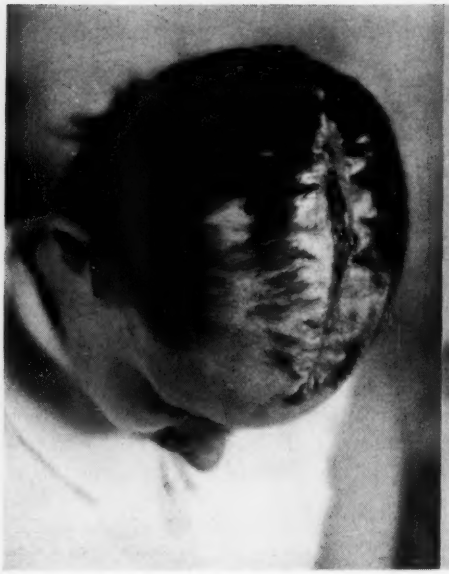

FIG. 3.—Result of second stage two months following the first stage as shown in Fig. 2.

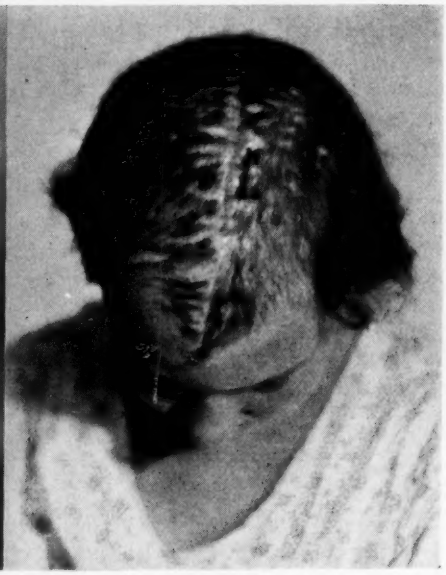

FIG. 4.—Showing result after third stage with complete closure of scalp and without distortion of face or ears.

across a hemisection of rubber tube drain, so as to maintain a constant tension on the margins of the scalp (Fig. 2). This procedure reduced the transverse diameter of the avulsed area to 6 cm., virtually one-half of its original size.

The patient's postoperative course was uncomplicated and she was discharged June 25, three weeks after admission to return at two-day intervals for dressing. She was readmitted August 9, 1933, two months after the accident, and a second stage operation, identical in procedure, was done August 12, 1933. The wound had now been reduced to a granulating area varying from 1 cm. to 3 cm. (Fig. 3). She was discharged August 23, 1933.

After nine months the contour of the head and facial expressions were normal despite the great stretching of the scalp, and the head was covered with normal hair. June 29, 1934, the remaining portion of scar tissue was removed, allowing an exact apposition of full thickness hair bearing scalp, with only a linear scar remaining as evidence of the loss of tissue from the head. (Fig. 4). Nine months later there were no evidences of defect and no distortion of features (Fig. 5).

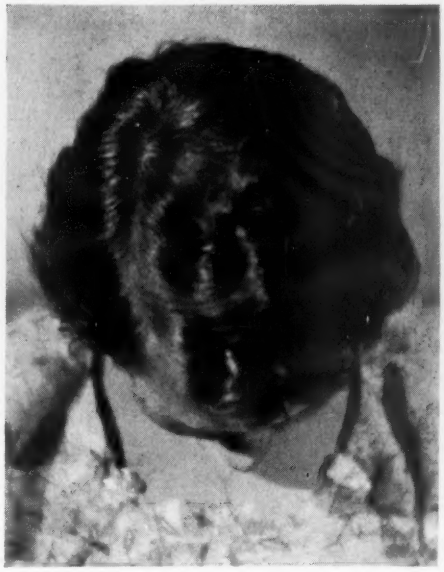

FIG. 5.—Showing result nine months after third stage without further operation.

CONCLUSIONS

(1) The scalp has moderate mobility and elasticity permitting marked stretching.

(2) The abundant blood supply of the scalp will permit marked suture tension without sloughing and resists infection.

(3) Many cases of extensive avulsion of the scalp can be successfully treated without grafting if the above principles are employed.

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A MODIFIED CORONAL INCISION

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THE coronal or so called autopsy incision is sometimes used when it is necessary to turn down bilateral, frontal osteoplastic bone flaps as in the Naffziger operation (intracranial orbital decompression for malignant exophthalmos).

The usual straight coronal ear to ear incision was made in several of our cases. In one patient an infection occurred at the end of the incision in which

the tissues had been devitalized due to the acute angulation which occurred when the scalp was kept reflected for a long period of time. Also difficulty was experienced in keeping the scalp far enough forward without the use of strong retraction so that the anterior edge of the flap could be made close enough to the supra-orbital margin.

The essential objection, however, to the straight coronal incision is that a very acute angle is formed in the end of the incision with a resultant strangulation of vessels in that immediate region after the scalp has been reflected. This results in damage to tissues and predisposes to wound infection. In Fig. 1, *a* and *b*, the straight type of coronal incision is shown. In the same figure

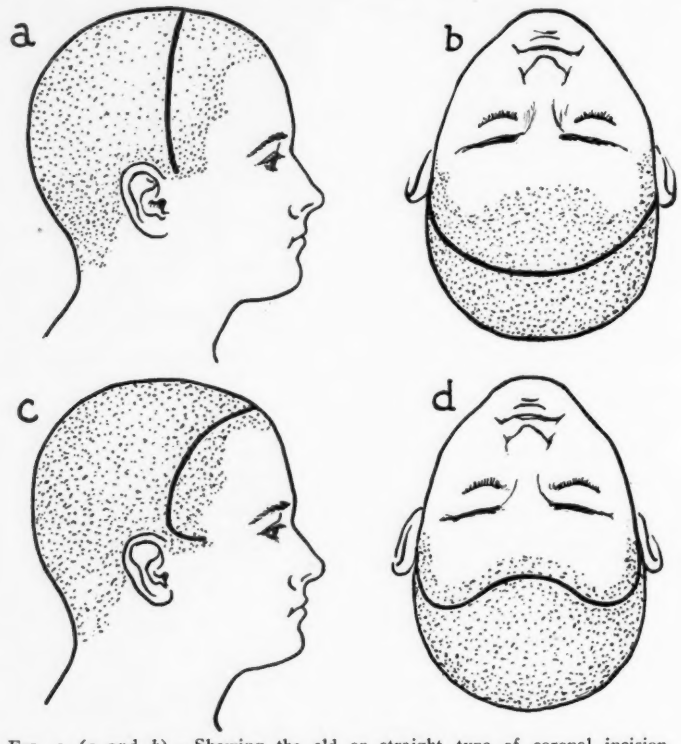

FIG. 1 (*a* and *b*).—Showing the old or straight type of coronal incision. (*c* and *d*) Showing the new or modified type of this incision.

c and *d* demonstrate the curved type which allows the scalp to lie in place without retraction after it has been reflected. As can be seen, the superficial temporal vessels are divided but adequate blood supply to the flap is assured through the supra-orbital vessels.

The incision is started about 3 cm. posterior to the external canthus of the right eye, practically at the level of the helix of the ear. The incision is kept about 2 cm. behind the normal hair line following its natural curve. Precautions are taken to carry the incision just through the aponeurotic fascia so that in reflecting the scalp by sharp dissection a fairly thick layer of subaponeurotic tissue is left. This facilitates suturing the osteoplastic bone flap

back in position and enables the burr openings in bone to be covered by this tissue, thus preventing unsightly depressions. If blunt dissection is used there is a tendency to strip the subaponeurotic tissue off the periosteum. The latter is frequently so fragile that it cannot be adequately sutured. Through and through suturing of the bone can be done but is not necessary if a sufficiently thick layer of subaponeurotic tissue is left. The latter was emphasized frequently by Cushing.

The advantages of the above incision are: (1) It causes less strain at the end of the incision, thus reducing the incidence of wound infection. (2) It allows the turning down of bilateral osteoplastic bone flaps without the use of retraction. (3) It gives a more adequate exposure in the temporal region during the bone work.

BOOK REVIEW

ATLAS OF PATHOLOGICAL ANATOMY. Compiled by E. K. MARTIN, M.S., F.R.C.S. Under the direction of the Editorial Committee of the British Journal of Surgery. Bristol, Eng., John Wright & Sons, 1930.

A work intended primarily for the general surgeon. In this volume are considered Tumors of Bone, Diseases of the Breast, Stomach, Kidney, Gall Bladder, Bile Ducts and Inflammatory Lesions of Bone. The illustrations are in color and monochrome and are uniformly good. They depict the lesions clearly and comprise both microscopic and gross lesions, the latter drawn from museum specimens. Although the author states no attempt was made to include the rarities and curiosities of surgical practice, several unusual specimens have been presented, namely, an unusual case of Syphilis of the Stomach and one of Polyposis with Intussusception of the same organ.

The concise histories with each case and the descriptive text concerning each specimen are especially valuable. No fault can be found with the general arrangement which conforms with the standard for this type of work.

It is the reviewer's opinion that the Atlas would be a valuable addition to the surgeon's library.

THOMAS A. GONZALES, M.D.

EDITORIAL ADDRESS

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